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EXPERIMENTAL STUDIES ON PRESSURE AND CONTRACTILITY IN THE URETER

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LARS BÄCKLUND

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EXPERIMENTAL STUDIES ON PRESSURE AND CONTRACTILITY IN THE URETER

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LARS BÄCKLUND

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Translated by

MAUD MARSDEN

Almqvist & Wiksells
BOKTRYCKERI AKTIEBOLAG
UPPSALA 1963

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CHAPTER I

Introduction

Historical review

The study of the physiology of the ureter has a long history, but it was not until the 19th century that the investigations took a more definite form. At first very simple methods were used, but keen observations were nevertheless often made. In 1869 ENGELMANN's first extensive reports on studies of the physiology of the rabbit ureter were published. ENGELMANN's study was limited to visual observations of the ureter, but in spite of this he was able to draw conclusions, some of which are still valid today.

The further development was partly due to improved technique. Intraluminal pressure measurement came into use at the beginning of this century, and a pioneer in this field was LUCAS (1905, 1906), who used an open water manometer. TRATTNER's hydrophoragraph (1924, 1932), which was used in a more or less modified form by several other workers, represented another milestone. One of these workers was LAPIDES, who in 1948 carried out investigations on the intact human ureter. In more recent years new potentialities for measurement have been introduced by advances in the field of electronics. It will suffice to mention here the great improvements resulting from the use of pressure transducers of different types. Further reference may be made to a review by FRY (1960), in which he discussed modern physiological recording instruments with particular regard to pressure measurement.

Electroureterography may be mentioned as one of the other methods of studying the physiology of the ureter. The first to record action currents from the ureteric musculature were ORBELI and VON BRÜCKE (1910), who used external electrodes. Remarkably enough there was for a long time little interest in electro-

myography of the ureter *in situ*, and it was not until the 1950's that this method became more generally adopted, intraluminal electrodes mainly being used. Classical studies on isolated segments had already been made earlier by Bozler (1942).

Considerable interest has long been paid to the anatomy of the ureter, and knowledge of the morphological conditions has to a certain extent influenced the interpretation of certain physiological events, especially as regards the conduction mechanism. Satani (1919 *c*) made a classical study of the microscopic anatomy. During recent years electron microscopy has been used, mainly perhaps in the search for an anatomical basis of a postulated conduction mechanism from cell to cell. As yet, however, certain problems, especially with regard to the innervation of the ureter, have not been completely solved. A review of the anatomical, physiological and pharmaco-dynamic factors which affect the activity of the ureter was made by Finkle and Smith (1955). Reference should also be made to a forthcoming review by Kiil (1963).

Modern views regarding ureteric function

Certain details concerning the function of the ureter were clarified at an early date. The occurrence of peristalsis has long been known, and similarly that peristalsis may be stimulated by urinary flow or other mechanical factors such as pinching and stretching. The possibility of stimulating the ureter electrically was also discovered early. On the other hand there has long been some doubt as to the way in which peristalsis is regulated and how the fluid transport is mediated. While the majority of workers have considered justifiably that the ureteric contents are driven forward by a propagating contraction wave, some have held the view that the ureter functions as a suction pump in which active dilatations produce the necessary under-pressure. The role of innervation in ureteric peristalsis seems to have been overestimated earlier, and in a series of studies with isolated segments Bozler, Prosser, Burnstock and others have shown that the conduction mechanism, at least, is independent of the nerve supply. The role played normally by the nervous components of the ureter must still be considered, however, as somewhat unclear.

Other essential problems in the field of ureteric physiology have concerned the origin of the peristaltic contraction wave in the upper urinary tract, and the conditions under which peristalsis is maintained. Some authors, in particular Narath (1951) have concluded that the contraction wave starts in the calyces of the kidney and passes downwards as a coordinated contraction wave along the pelvis and ureter. Others have doubted this view, especially in consideration of the fact that the calyces and pelvis or the pelvis and ureter appear to contract independently of one another. The existence of a regular pacemaker for ureteric peristalsis has also been claimed by several authors.

The pressure levels within which ureteric peristalsis can occur have been considered to be fairly limited, and the increase in pressure necessary for the initiation of a ureteric contraction has been assessed at varying levels (see further chapter II). Most of the authors who have studied the effects of high intraureteric pressures seem to be of the opinion that when there is a sufficient degree of distension the contractile ability of the ureter ceases. The pressure level required to produce such critical distension has been reported differently in different experiments. Risholm *et al.* (1959) expressed very interesting views on the relationship between high pressure and ureteric dilatation. They stated that the decrease in amplitude in the contraction-induced pressure waves with increase in the resting pressure was due to pressure damping in the fluid-filled renal pelvis. It has been one of the aims of the present investigation to consider further this hypothesis. Intraureteric pressure, ureteric diameter and electromyograms have been recorded in the dog and problems concerning the relationship between intraureteric pressure and contractility under different conditions have been studied. Perfused ureters *in situ* and also ureters with intact pelviureteric communications have been studied. Investigations have also been made with divided and re-anastomosed ureters *in situ* with the purpose of studying the conduction mechanism in the smooth muscle of the ureter.

CHAPTER II

Perfusion of the ureter in situ

There have been relatively few modern studies concerning muscular contractility during perfusion of the ureter. Isolated ureters or ureteric segments have been generally used. Murnaghan (1957) studied the dynamics in isolated ureters from human beings and pigs at low and moderate perfusion pressures. Gould *et al.* (1955 *a*) used isolated ureters from water buffaloes, and Atwell and Borgstedt (1960) investigated the peristaltic reflex in isolated dog ureters. Satani (1919 *b*) and Sleator and Butcher (1955) perfused the dog ureter *in situ*. The latter simultaneously recorded action potentials with intraluminal electrodes. No investigations appear to have been made on the maximal height to which the intraureteric pressure can be forced while yet retaining contractile activity in the ureter. There appears to be some divergence of opinion as regards both the magnitude of the resting pressure in the renal pelvis and the ureter, and the pressure level required to induce peristalsis. Pressure levels between 0–2 cm and 12–15 cm of water respectively have been claimed (Durand and Descotes 1952, Davis 1954, Murnaghan 1957, Kiil 1957, Fink and Murphy 1957, Weinberg and Siebens 1958, Atwell and Borgstedt 1960, Weinberg and Maletta 1961). In those cases where both man and dog have been investigated with the same methods, fairly similar conditions have been found in these two species. No studies appear to have been made, on the other hand, as to whether the rate at which the peristalsis-inducing pressure level is reached is of any importance in hastening or delaying the commencement of peristalsis. Since, however, an ability of the ureteric tissue to exhibit adaptation with a slowly rising intraluminal pressure cannot be excluded *a priori*, one aim of the present investigation was to determine whether there is any difference in the induction mechanism for peristalsis when the perfusion pressure is increased at two different rates. Intact com-

munication between the renal pelvis and the rest of the ureter probably plays an important part in normal peristaltic function, but for reasons given below it has been considered of value to test the activity of the ureter when isolated from direct connection with the renal pelvis. The investigation has also aimed at studying the reactions of the ureter when the pressure rise is continued above the level at which peristalsis is induced, and the extent to which the contractile responses are altered with increasing pressure. The generally accepted view that the ureteric contractions cease on high intraureteric pressure appears to be a consequence of the partial unsuitability of the older methods. With these older methods it was not possible to identify the ureteric contractions in conditions of ureteric dilatation and open communication with the renal pelvis. This motivated perfusion studies with as little pressure-damping effect as possible in the perfusion system.

Material and methods

Fifteen adult mongrel dogs of both sexes and weighing between 10.5 and 28 kg were used in the experiments. The anaesthetic used was sodium pentobarbitone (veterinary Nembutal®, Abbott), 30 mg/kg body weight being injected intravenously, followed by tracheal intubation. For the administration of diuretics and in case further anaesthetic was required to maintain the required depth of anaesthesia, a catheter was inserted routinely into a femoral vein. The abdomen was opened with a mid-line incision and both ureters were cannulated distally, near to the bladder, with polythene catheters with an outer diameter of either 1.5 or 1.6 mm and a lumen of either 0.9 or 1.1 mm, depending on the ureteric dimension. After cannulation the abdomen was closed. In the majority of the experiments the arterial pressure was recorded with a pressure transducer connected to a catheter in the left femoral artery, and the respiration was recorded intermittently by connecting the tracheal tube to a Krogh spirometer filled with oxygen. The movements of the oxygen clock were transformed by means of a rotatory potentiometer to electrical potential differences. The ureteric pressure was recorded through the catheters by pressure transducers, the outflow from the ureter

being obstructed. The transducer used was an Elema Type No. EMT 472 a (Elema-Schönander, Solna, Sweden), which has a volume displacement of 0.3 mm^3/100 mm Hg and is linear in the region 0–300 mm Hg.

As a rule only one ureter was studied in each experiment, the other serving as a control for the extent of the diuresis. In the first part of the experiment the pressure and peristalsis were studied in ureters where communication with the kidney was intact. Sodium chloride solution 0.9 % was given intravenously as a diuretic, in doses of 10–40 ml, sometimes repeated. The abdomen was then reopened and the "experimental" ureter divided close to the renal pelvis. A perfusion catheter was inserted into the distal side of the cut ureter (i.e. the proximal end of the now isolated ureteric segment), care being taken to minimize damage to the vascular supply of the ureter. In order to protect the catheter as far as possible from movement artifacts, it was passed through a slit in the flank. In its course through the belly wall the catheter ran loosely through a short rigid plastic tube of greater diameter. The mid-line incision in the abdomen was then again closed. The perfusion catheter was connected via a long non-elastic tube to a glass burette placed horizontally, which at the commencement of the experiment was adjusted exactly to the level of the ureter. The burette could be raised by an elevator at two different rates, i.e. 13.2 mm/min or 82 mm/min. This made it possible to increase the perfusion pressure at rates of 0.97 mm Hg/min and 6.05 mm Hg/min respectively. Sodium chloride solution 0.9 % at room temperature (22–24°C) served as the perfusion fluid. During the passage through the perfusion catheter, however, the solution became warmed, since the abdomen was closed and the rate of flow was low. The flow from the burette was closed off intermittently by means of a tap. This tap was situated in the burette and was closed by turning 45°. No volume displacement in the perfusion system occurred on closing the tap.

In the majority of experiments the perfusion pressure was recorded with a transducer, which was connected to the perfusion catheter by a three-way tap. In the remaining cases the hydrostatic pressure was determined by measuring the difference in level between the burette and the ureter. An optical oscillograph was used for recording, with mirror galvanometers (Ruhstrat)

and two cameras, one with a slow film speed for continuous, and one with a high film speed for intermittent, rapid recording. In the experiments where the arterial blood pressure was not measured, an ink writer (Varian G-10) was used for the ureteric pressure recordings, together with a D.C. amplifier (pH-meter PHM 22, Radiometer, Copenhagen, with specially modified input and output connections).

Results

With intact pelviureteric connections

Eighteen experiments were performed in all. In two cases satisfactory ureteric activity was not obtained. In the other sixteen cases the experiments were performed with the technique described above. When a ureter with intact renal communication was occluded, it was a constant finding that when the basal pressure rose the amplitude of the pressure waves increased first, followed later by an increase in the frequency. With a progressively increasing basal pressure the amplitude of the pressure waves decreased and finally became so low that the contractile activity in the ureteric muscles could no longer be identified as peristaltic pressure waves. *With a sufficiently high pressure only pulse-synchronous pressure oscillations were observed in the ureter.* This condition usually occurred at an intraureteric pressure level of 25–30 mm Hg. In exceptional cases large pressure wave amplitudes due to contractions were found even with higher pressures. This appeared to be more common in young dogs and puppies. A typical course in the ureteric pressure curve after occlusion may be seen in Fig. 1. After intravenous infusion of sodium chloride the ureteric pressure rose regularly but no other important change was noted in the pressure curve.

Perfusion at low pressures (below 15–20 mm Hg)

In the perfusion experiments the pressure increase was not started until any residual fluid had been emptied out of the ureter. In half of all the experiments contractions which may have been provoked by irritation caused by the indwelling catheters were observed. In two cases these contractions could not be stopped even after a long waiting period. There appeared

to be no correlation in this respect between the size of the ureter and that of the catheter inserted. Large ureters often reacted to a catheter which in other experiments had been inserted into a smaller ureter without causing irritation. With the slow pressure increase (0.97 mm Hg/min) it was found that in all cases except three, which will be described separately below, *ureteric peristalsis commenced at pressures between 1–2 and 16 mm Hg.* As soon as peristalsis had definitely started and with regular frequency, the experiment was discontinued and the perfusion pressure reduced again to zero, after which the ureter was allowed to empty itself freely. Only small quantities of fluid (0.4–1 ml) ran from the burette into the ureter during the experiments. When the ureteric activity appeared to have ceased once more, a new perfusion was commenced with a rapid increase of pressure (6.05 mm Hg/min). There again the peristalsis started at approximately the same pressure level as with the slow pressure increase. In several cases there was no difference, and on a few occasions the peristalsis was produced at lower pressures during the slow increase in pressure. The three cases that had reacted differently with the slow increase also deviated from the typical response to a rapid increase of pressure. On the whole they reacted more slowly; with a rapid rise in pressure the contractions did not start until the pressures reached 20, 25 and 50 mm Hg respectively, and with the slow rise 40, 30 and 70 mm Hg respectively. The ureter that did not start contracting until the pressure had reached the considerably raised level of 50 mm Hg was found on examination at the end of the experiment to have thickening of the muscle layer, and pronounced trabeculation and a thickened mucosa in the bladder. In the subsequent part of the experiments, however, none of these three ureters differed from the rest of the ureters included in the material.

Perfusion at high pressures

On continued increase of pressure above the level at which the ureteric contractions had begun, *two principal activity patterns were observed.* Either the contractions occurred regularly with frequencies of about 5–10/min, or 6–8 contractions were observed to alternate with inactive phases of varying length. The latter was most commonly seen. Regardless of the pattern exhibited by

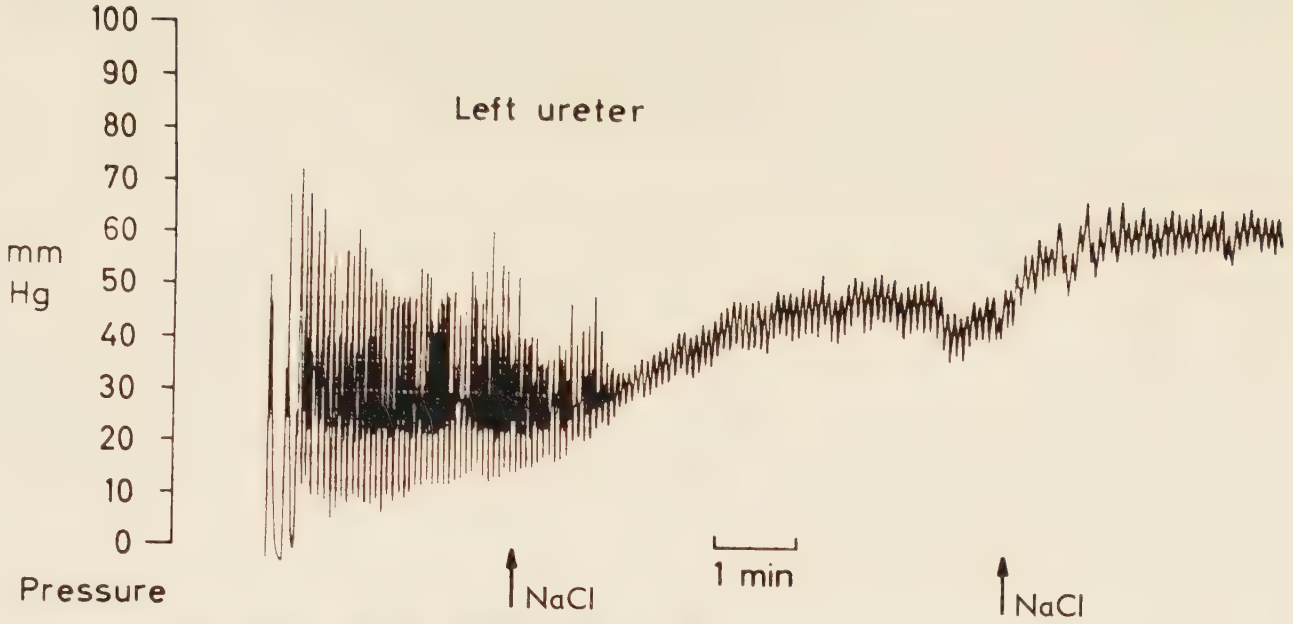


Fig. 1. Ureteric pressure variations after total occlusion of the distal end of the ureter. (Pelviureteric connections intact.) The basal pressure, which is represented by the minimum value of each pressure wave, rises rapidly. The character of the curve changes at a pressure of about 30 mm Hg, when the amplitude of the pressure wave, induced by the contractions, becomes too small to be measured. The ureteric pressure subsequently varies synchronously with the respiratory movements and the arterial pressure which are not recorded in the picture but were observed visually. The increase in pressure resulting from intravenous injections of 0.9 % NaCl solution can also be seen. Recorded with an ink writer.

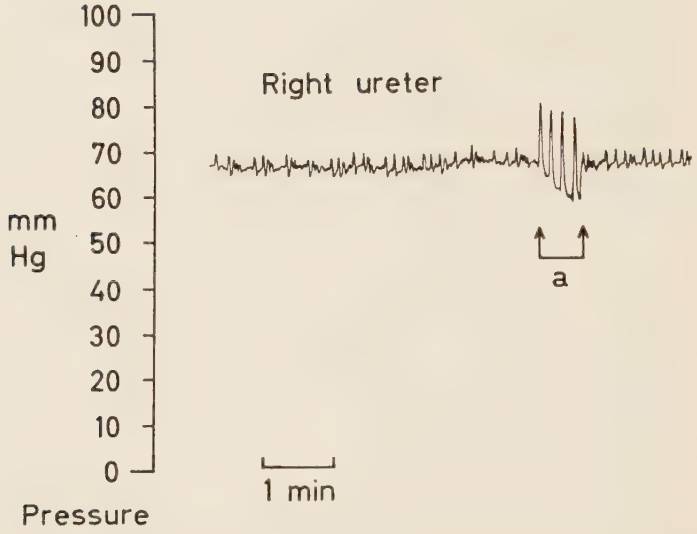


Fig. 2. Pressure recording from an experiment in which the ureter was perfused in situ. There are small, somewhat irregular, pressure variations; their amplitude was increased markedly during the time the burette used for perfusion was closed (*a*). Recorded with an ink writer.

the individual ureter, both the frequency and the amplitude of the pressure waves decreased with increasing perfusion pressure. When the pressure was again reduced, the contraction frequency and the amplitude increased again. In several cases, however, both the amplitude and the frequency were lower while the pressure was being reduced than at the corresponding level during pressure increase. The maximal perfusion pressure that could be applied without loss of the contractile power varied between 50 and 125 mm Hg. In five cases the pressure was 100 mm Hg or more. The ureters were thus capable of functioning for a fairly long period with high intraluminal pressures. In the majority of the experiments the perfusion pressures were maintained for an hour or more.

At different pressure levels the burette tap was closed, and the ureteric pressure wave could not then be transmitted to the free fluid surface of the burette. *It was found constantly that the pressure wave amplitudes then increased markedly.* Fig. 2 shows the ureteric pressure curve before and after closing of the tap. *The contraction frequency was unchanged but the pressure*

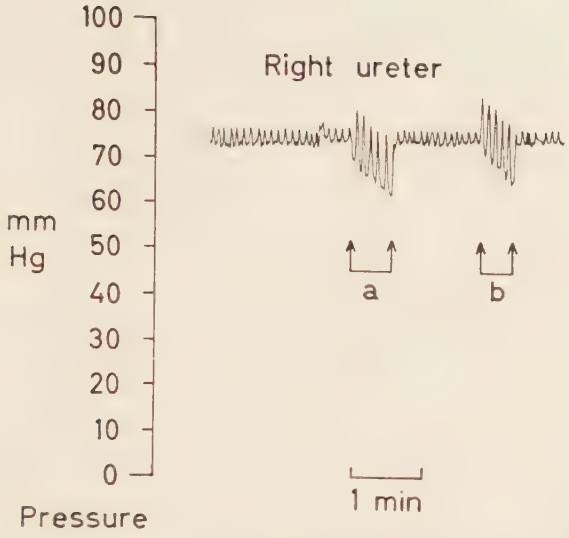
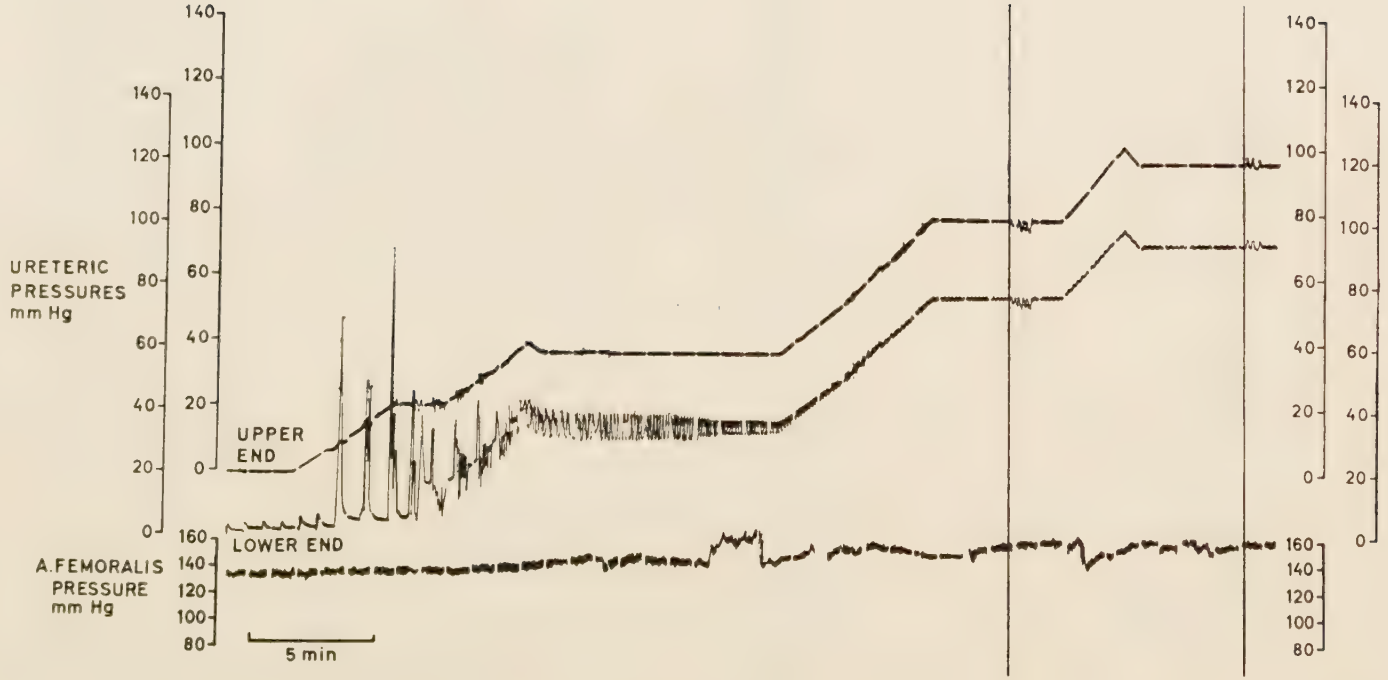


Fig. 3. The same experiment as in Fig. 2, but with a higher pressure and later. There has been a stasis of long duration with a perfusion pressure maintained at over 40 mm Hg for 60 minutes. There were regular contractions, the pressure wave amplitudes of which rose markedly during the two periods when the perfusion burette was closed (*a*, *b*). When the burette was closed the basal pressure fell due to leakage from the catheter.

wave amplitude increased when the tap was closed. Fig. 3 illustrates the persistence of contractility even on prolonged intraureteric hypertonia. Fig. 4 shows a perfusion experiment with a rapid pressure increase. The amplitudes of the pressure waves are seen to decrease on rising pressure and are hardly distinguishable at 95 mm Hg before the burette is closed off (Fig. 4 *b*).

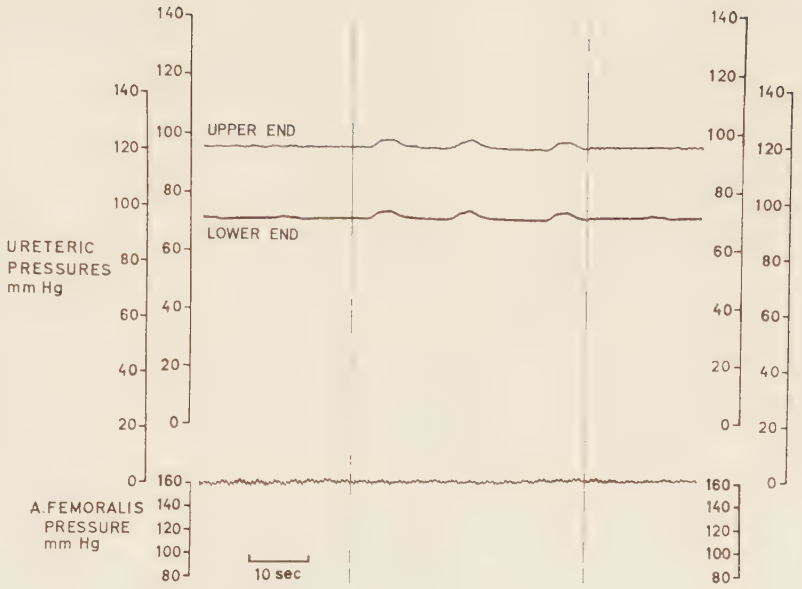
During the periods when the respiration frequency was recorded, *no relationship between respiratory movements and ureteric peristalsis could be shown.* The frequencies sometimes coincided without this changing the peristaltic pattern or shortening the phases of inactivity.

With the system used perfusion pressures higher than 155 mm Hg could not be applied, and any remaining pressure variations due to contraction could not be distinguished with certainty from artifacts due to respiratory movement or other external disturbances exerting pressure against the ureter or the indwelling catheter. In tests to find out how high a pressure dog ureters can


URETERIC
PRESSURES
mm Hg
UPPER
END
LOWER END
A.FEMORALIS
PRESSURE
mm Hg
5 min
140
120
100
80
60
40
20
0
160

a

Fig. 4. Perfusion experiment recorded with an oscillograph and showing the pressure in the perfusion catheter (upper end) and distally in the ureter (lower end). Fig. 4*a*, recording with a slow film speed; Fig. 4*b*, recording with a higher film speed at the time of the second vertical line in Fig. 4*a*. In the slow recording it can be seen how peristalsis increases successively in frequency while the amplitude decreases with rising pressure. At about 60 mm Hg the amplitude is very small. The perfusion burette was closed at both the vertical lines in Fig. 4*a*, resulting in a temporary increase in the pressure wave amplitude which declined again when the burette was reopened (not marked). The difference in the pressure wave amplitude is better seen on the rapid recording when the burette was closed between the two vertical lines.
Note the double ordinate scale. The pressures in the upper and lower ends were the same. The pressure impulses from the femoral artery were damped, giving a mean value.



b

tolerate without rupture, a fluid pressure corresponding to 370 mm Hg was applied in two cases without any leakage or macroscopic damage being caused. Not until the pressure was increased to a level well beyond the response range of the transducer did the ureteric walls rupture.

Discussion

Peristaltic patterns

The peristaltic pattern of the ureter after acute total occlusion and with intact pelviureteric communication involves firstly increasing basal pressure, followed by increase in the amplitude and the frequency of the pressure waves. The latter increase especially at pressures of about 10–15 mm Hg. Similar observations have been made by several other authors. Initial increases in frequency and amplitude are described by Gould *et al.* (1955 *b*), among others. It has been discussed whether increased ureteric flow results in an increase in tone alone (Morales *et al.* 1952) or also in an increase of frequency (Hanley 1953). With further rise in pressure the amplitude of the pressure waves decreases progressively (Trattner 1932, Lapides 1948, Kiil 1957, Risholm *et al.* 1959, Boyarsky and Martinez 1962, and others). The interpretation offered by most authors for this finding is that the activity of the ureteric musculature gradually ceases with increasing distension, and that under normal conditions the urine would flow out of such a ureter by virtue of the pelvic pressure. Morales *et al.* (1952), who studied the reactions of the ureter at different flow rates, stated that with a high flow the ureter is so dilated that no contractions are possible. With sufficiently high intraluminal pressure the whole ureter becomes dilated, and free fluid communication is established with the renal pelvis. Boyarsky and Martinez (1962) have demonstrated this by means of urography. It has been often found that when there was an open fluid communication in the upper urinary tract ureteric pressure oscillations were completely synchronous with the arterial pulse and there were no visible pressure peaks due to contraction. This phenomenon has been described previously by several authors and will be discussed in more detail in chapter III. This free fluid

communication occurs fairly constantly at 25–30 mm Hg in dogs. This agrees with the conclusion of Henderson (1905) that in dogs the ureteric contractions disappear at pressures corresponding to 26–32 mm Hg.

A few workers, however, have also described ureteric contractility at higher intraluminal pressure levels. Trattner (1932), in experiments with his hydrophoragraph, found that contractions died out at a level of 38–70 cm water. Gould *et al.* (1955 *b*) noted ureteric contractions at 50 cm water when the pressure was forced to increase by manual compression of the urinary bladder. Sleator and Butcher (1955) recorded action potentials from ureters during perfusion with pressures up to 25–30 cm water. The peristaltic waves were then at a maximum and tended to come in groups. Davis (1957) stated that the peristaltic waves disappeared completely at pressures above 54 mm Hg. Reports on the contraction ability in isolated, perfused ureters at still higher pressures have been published by Lucas (1908), who observed that a segment of a dog ureter was capable of raising a column of Ringer's solution 92 cm, and Murnaghan (1958) who demonstrated the activity in a megaureter at pressures of up to 80 cm water.

The damping effect of the renal pelvis

Risholm *et al.* (1959) observed strong ureteric activity at pressures of about 40–45 mm Hg when the open communication between the renal pelvis and the ureter was interrupted with a ligature. They considered that the ligation simply eliminated a damping effect of the pelvis. The procedure of closing off communication with the pelvis by a ligature involved, however, some displacement of fluid into the ureter. It is conceivable that this might involve a trigger effect by causing extension of the ureteric walls. It is thus not precluded that a temporarily extinguished peristalsis can be re-started in this way. Closing off with the burette tap does not change the fluid content in the ureter, and is therefore a better method. After closing, the ureter appeared to retain its tension, since the pressure recorded in the perfusion system remained unaltered or decreased only very insignificantly.

The damping theory put forward by Risholm seems to agree well with the present results. *If the natural renal pelvis is eli-*

minated and perfusion is carried out from an artificial "renal pelvis" with rigid walls in the form of a glass burette, it should be expected that pressure variations due to contractions would be found at pressure levels where no pressure waves can normally be identified in the ureter. The results found in the experiments are in agreement with this supposition. It is true that the amplitudes decrease progressively, but the damping had not been completely eliminated in the system. In closing off the burette with the tap, however, damping should be decreased further even if it does not disappear entirely, and the results obtained with an increased pressure wave amplitude at the moment when the burette was closed, clearly confirm this assumption. *It is thus clear that on perfusion of an isolated ureter pressure waves due to contraction can still be found at 100–125 mm Hg. If this ureter were in free fluid communication with the renal pelvis, however, it would exhibit the classical reaction of decreasing pressure wave amplitudes and, at 25–30 mm Hg, "cessation of peristalsis".* The muscularly weak renal pelvis does not appear to be able to resist large pressure increases, and a damping effect due to regurgitation of fluid is therefore obtained as soon as an open communication has been established.

A certain degree of damping, however, must also take place in the ureter. Since the whole organ does not contract simultaneously, a rapid pressure wave distribution takes place in the fluid-filled dilated ureter, and the temporarily inactive parts become able to distend further. A perfusion technique such as that used here, with pressure measurement alone, is therefore not perfect for determining the level to which the pressure can be raised with retention of contraction ability. The boundary line as regards the power of the ureteric muscles to contract against progressively increasing pressure has not yet been determined. It is clear, however, that it exceeds that pressure that may possibly occur in the ureter in physiological or pathological conditions. Further, there must be a considerable margin between the pressure which can be overcome by the muscles and that which the muscular and elastic elements in the ureteric wall resist in a purely passive way before rupture and macroscopic breaks occur. In two control experiments a pressure of 370 mm Hg was exerted without any rupture of the ureter. Corresponding experiments

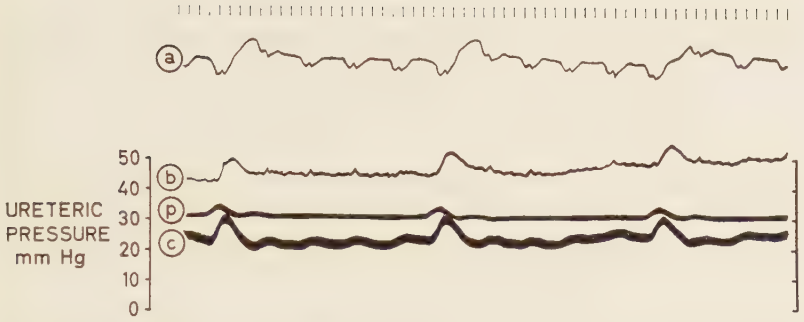


Fig. 5. Retrograde peristalsis during ureteric perfusion. Simultaneous recording of the ureteric diameter at three different points (*a*, *b* and *c*). Point (*a*) was situated nearest to the kidney, and (*c*) nearest to the bladder. The large upward deviations indicate contractions. (*p*) is the pressure in the ureter distal to (*c*). The pressure increases begin before the contractions at (*c*), which in their turn appear before the contractions at (*b*), etc. There are small respiration-induced variations in ureteric diameter. The time intervals in seconds are marked in the uppermost part of the figure. Recording with a Visicorder.

on human ureters (Boone and Smith 1955) showed pressure tolerances up to 200 mm Hg without any change in the elastic properties of the ureteric wall.

Peristalsis at high pressures

The question of whether the contractions shown by the ureter at high pressures constitute a peristaltic wave running the length of the whole organ, or an antiperistaltic wave, or whether these are merely local strong contractions, cannot be answered using the method described. At low pressures there is probably a normally propagated peristaltic wave, since fluid movement was constantly observed in the glass burette a few seconds before the pressure increase was recorded in the distal part of the ureter. It is probable that the pelviureteric communication is of great importance for the initiation of normal peristaltic waves. The existence of a pacemaker for the peristalsis has been suggested by many authors, and will be discussed in detail in Chapter III. In perfusion experiments on the rabbit (Bäcklund, unpublished data) it was found difficult to produce peristalsis when the communication between the pelvis and ureter was broken. In dogs it is clearly possible to initiate a contraction wave merely by a

proximal pressure increase. At high pressures there is a dilated ureter with free fluid communication between the two pressure transducers, and the pressure wave is therefore recorded at practically the same time in both places. In some experiments there was, however, a tendency towards an earlier rise in pressure distally, which either indicated antiperistalsis or that only the distal part was contracting. Many authors have also maintained that the distal third of the ureter is last in ceasing to contract on rising pressure (Lapides 1948, Murnaghan 1957). Fig. 5 shows a perfusion experiment with a modified technique in which the ureteric diameter was recorded in three different places. For the method reference may be made to Chapter III. The contractions appear to travel in a *retrograde* direction. Observations of peristalsis after division of the ureter were made by Shiratori and Kinoshita (1961 *b*). They found that when the ureter was divided at the pelviureteric junction retrograde peristaltic waves running through the whole ureter occurred.

The relation between perfusion pressure and contractile response

The magnitude of the perfusion pressure at the commencement of peristalsis in the individual ureters varied. In the two cases where there was spontaneous peristalsis, it is possible that the catheters caused irritation that stimulated contractions. The effect of an indwelling catheter on ureteric peristalsis has often been discussed, and it has been questioned especially whether free flow and normal peristalsis can remain undisturbed under these conditions (see Kiil 1957, for further references). Trattner (1932) described spasms after the insertion of catheters. The spasms ceased within a few minutes, however, either spontaneously or on intraureteric injections of sodium chloride. It seems reasonable to believe that irritation from catheters was of secondary significance in these perfusion experiments. In the great majority of cases an intraluminal rise in pressure and ureteric distension are required to produce peristalsis. There are individual variations in the magnitude of the contractile response, and this probably partly explains the relatively wide distribution obtained in this investigation, and also the divergent results obtained in previous studies. Neither does extension sensitivity appear to be noteworthily different in the slow pressure increase used, com-

pared with the rapid increase. It is possible that a difference would be observed if a pressure increase were induced at a rate of, for example, 0.1 mm Hg/min, and that the muscle cells would then have time to become "adapted". The effect in this case would be that contraction would appear first after a greater amount of distension than when a rapid but small pressure increase was produced. This will be discussed further in chapter VI.

CHAPTER III

The contractility at high intraureteric pressures with intact pelviureteric connections

As already mentioned in the previous chapter, the decrease in amplitude of the ureteric pressure waves associated with increase in intraluminal pressure has been interpreted by the majority of workers as due to a weakening and finally an inhibition of peristalsis. Since, however, the perfusion experiments showed that muscular contractility can occur even at very high intraureteric pressures, a series of experiments was performed, the purpose of which was to study the relationship between pressure and ureteric muscular activity when the pelviureteric connections were intact, and where more criteria for ureteric contractions than pressure waves alone were required.

Material and methods

Altogether sixteen adult dogs of both sexes and weighing between 8.5 and 25 kg were used for the experiments. They were anaesthetized with intravenous injections of veterinary Nembutal® (Abbott) in a dosage of 30 mg/kg body weight. The left femoral vein was cannulated to facilitate intravenous infusions. A catheter was inserted into the right femoral artery for recording the arterial pressure with a pressure transducer or a mercury manometer. Either an oxygen-filled Krogh spirometer, adapted as described in chapter II, or a balloon placed under the diaphragm and connected to a pressure transducer for marking abdominal pressure variations were used for pneumotachography.

The abdomen was opened with a long mid-line incision from the ensiform process to the symphysis pubis. After puncturing and emptying the urinary bladder both ureters were cannulated as near to the bladder as possible, great care being taken to

minimize damage to the vascular supply to the ureter. Polythene tubes with terminal holes and with an external diameter of either 1.5 mm or 1.6 mm and an inner diameter of 0.9 mm or 1.1 mm respectively were used as catheters. The catheters were inserted about 1 cm proximally and were secured with a ligature. After cannulation the ureters were allowed to drain for a few minutes for estimation of the diuresis on each side. In the case of very slow ureteric flow rates 0.9 % sodium chloride solution was administered intravenously in doses of 10–40 ml, to increase diuresis. When a satisfactory flow of urine was obtained, one of the ureters was connected to a pressure transducer (Elema EMT 472 a, see page 10), and the ureteric pressure was recorded during a few minutes' occlusion to assess the ureteric activity. The stasis was then released and an electrode inserted into the wall of the ureter 0.5–2.5 cm above the tip of the ureteric catheter. In a number of experiments a piece of silver wire about 0.1 mm thick, isolated but for the tip surface in a glass capillary the outer diameter of which varied between 0.2 and 0.35 mm, was used as an electrode. A small piece of fine-mesh earthed iron net, placed under the ureter, served as a reference electrode. In the remainder of the experiments a concentric needle electrode (13 K 51, Disa Elektronik A/S, Herlev, Denmark) was used. The Disa electrode was 30 mm long with an outer steel sheath of 0.45 mm diameter and an inner isolated platinum wire, the active area of which was approximately 0.04 mm^2. The steel sheath served as the reference electrode and was earthed. In all of the experiments a special earthed electrode was also inserted into the left hind leg of the animal.

Eighteen experiments were performed altogether, and in thirteen of these the changes in the ureteric diameter were recorded with an indicator constructed specially for the purpose (Fig. 6 *a*). The claws of the indicator were placed around the ureter at the level where the electrode had been inserted (Fig. 6 *b*). In two experiments a further indicator was also placed 25–30 mm proximally to the electrode. Both the electrode and the diameter indicators were held in position by being clamped to rigid bars, and in order that the abdominal viscera should not displace the measuring instruments, the viscera were packed in muslin compresses wet with sodium chloride and held aside by hooks.

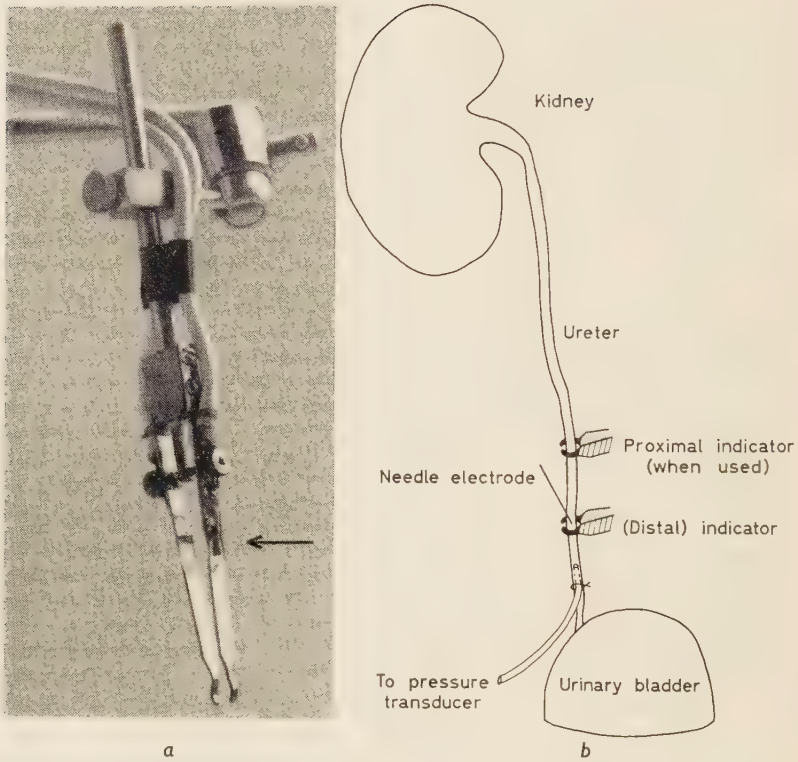


Fig. 6. Indicator for measuring variations in ureteric diameter (*a*). It consists of two tongues of phosphor bronze, 10 cm long and 0.6 cm broad. They are attached, at one end, to a wedge-shaped brass block. Their free ends are narrower and shaped so that together they resemble a claw. At the arrow the tongues are ground thin so that they are very flexible. Strain gauges coupled as part of a bridge are mounted on the thin regions of both tongues. The tongues have some resilience, but very little force is required to move them, and all bending occurs at the thin regions. The movements are thus transduced via the strain gauges into electrical information. With the aid of two screws placed just above the thin regions, the claws can be adjusted so that they just enclose and very lightly touch the ureter. The instrument thus subsequently follows radial variations in the ureter. The schematic diagram (*b*) shows where these indicators were placed.

When all preparations were complete, the ureter was totally occluded by connecting the catheter to the pressure transducer, and the ureteric pressure, action potentials (AP) and diameter variations were studied at the same time as also were the arterial pressure and respiration. An attempt was made to obtain an intraureteric pressure sufficiently high to ensure free fluid com-

munication between the renal pelvis and the ureteric catheter. When necessary the diuresis was stimulated with sodium chloride infusions. In seven of the experiments succinylcholine iodide (Celocurin® iodide Vitrum) in a dose of 1 mg/kg body weight was administered intravenously to produce total blockade of the striated muscle.

The recording apparatus varied somewhat. The electromyogram was recorded via a cathode follower either on a two-channel oscilloscope, with or without simultaneous recording of the diameter variations and photographed with a Du Mont Polaroid Land camera, type 2620, or together with all the rest of the traces on a multichannel recorder. The input time constant of the cathode follower was 4 μsec and the amplification factor 0.83. The active electrode was connected by a double-shielded cable to the grid of the cathode follower tube, and the inner cable shield to its cathode. The outer shield was connected to the reference electrode and earthed. By using a shield connected to the cathode the capacitative effects in the electrode cable are kept as low as possible, thus improving the signal reproduction.

In most of the experiments an optic oscillograph (described in chapter II) was used as a writer; in the other experiments a fourteen-channel oscillograph of the Honeywell Visicorder type 906 A–1 was used, with D.C. amplifiers (Grass Low Level Preamplifiers) for the ureteric pressure transducer and diameter indicators.

Results

The time course of the ureteric peristalsis after occlusion showed the same pattern as in the experiments described in chapter II. After a period of increasing frequency and amplitude, the amplitude of the pressure waves again decreased with increasing pressure. As a rule, when there was free fluid communication between the renal pelvis and the ureter, only pressure oscillations synchronous with the arterial pulse and other arterial pressure variations were obtained.

An action potential occurred constantly before each pressure wave, and as an expression of ureteric contraction a decrease in the diameter of the ureter was obtained after each action potential. The close relationships between action potentials, ureteric

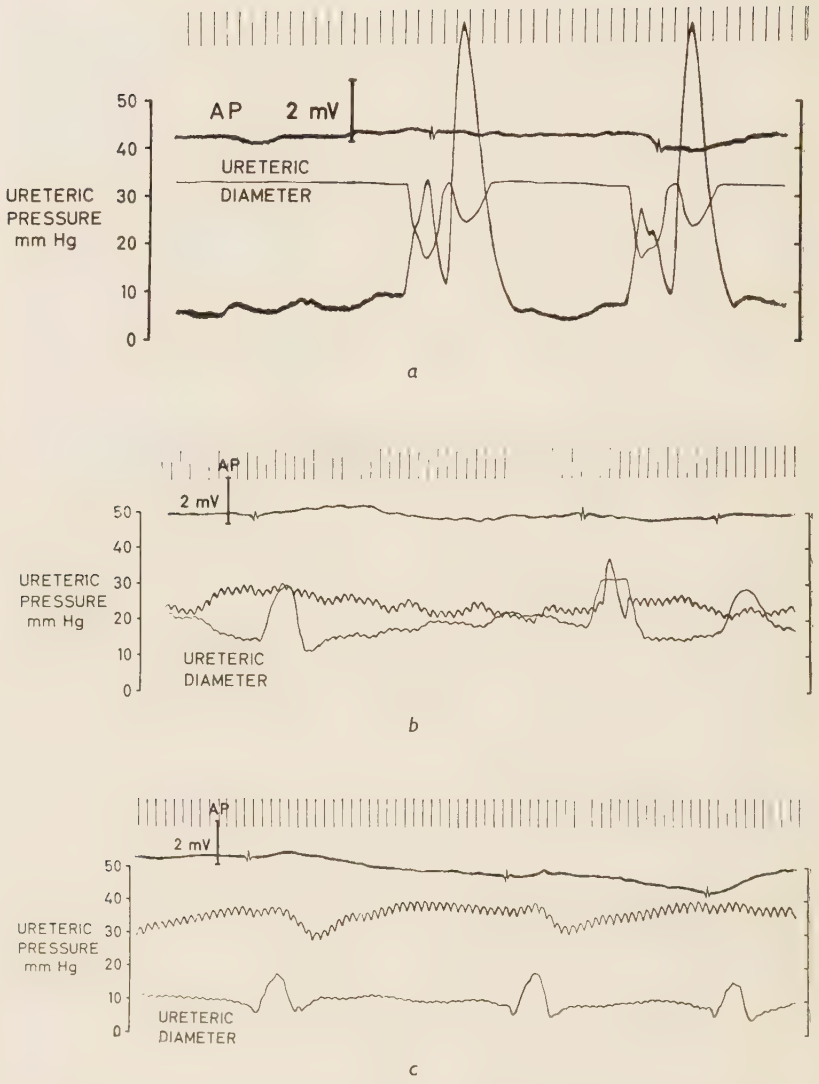


Fig. 7. The relationship between the action potential and the variations in ureteric diameter and pressure. (Pelviureteric connections intact.) Upward deviations in the diameter recording indicate contraction and downward deviations, dilatation. The curve in Fig. 7*a* is discussed in more detail in Chapter IV. Note that in 7*b* the ureteric pressure rises with the second contraction (incomplete damping). In both 7*b* and 7*c* the ureteric pressure varies synchronously with the arterial pulse and respiration. The latter were studied visually and are not recorded here. The large periodic decreases in ureteric pressure in 7*c* are due to respiration. The uppermost marks are time intervals in seconds. Recordings with Visicorder.

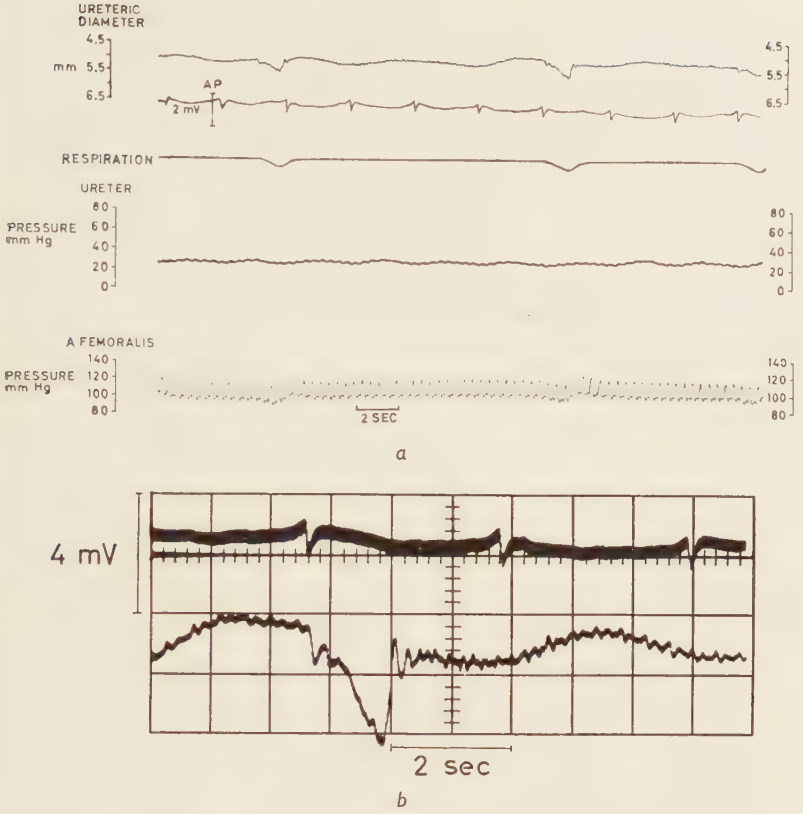


Fig. 8. Regular contractions in a ureter with intact pelviureteric connections and a pressure of 25–30 mm Hg. There are small pressure variations synchronous with the arterial pulse together with a small and regular increase after each action potential. The diameter recording also shows respiration-dependent changes. (Optical oscillograph.) Fig. 8*b* shows cathode ray oscilloscope traces of action potentials (above) and diameter variations at the time of the second respiratory movement in Fig. 8*a*.

contractions and pressure increases at moderate intraureteric pressures (5–20 mm Hg) were studied separately and are treated in chapter IV.

With pressures of over 25–30 mm Hg the pressure wave amplitudes became so small that they could not be identified with certainty. *The action potentials and ureteric contractions, however, continued to occur with an essentially unchanged appearance.* The different parts of Fig. 7 show the ureteric activity at different intraluminal pressures. With low pressures (Fig. 7 *a*)

TABLE 1. *The frequency of ureteric contractions immediately after the beginning of occlusion (initial frequency) and then after two consecutive periods.*

Experiment No.	Initial frequency per min	Occlusion time in min	Final pressure in mm Hg	Final frequency per min	Occlusion time in min	Final pressure in mm Hg	Final frequency per min
1	*17*	34	30	*20*	70	50	*15*
2	*10*	23	30	*8*			
3	*18*	28	40	*10*	43	50	*9*
4	*9*	3	35	*20*	17	45	*20*
5	*8*	32	30	*24*	56	45	*10*
6	*12*	50	30	*10*	90	30	*6*
7	*30*	60	55	*20*	150	60	*6*
8	*17*	30	45	*17*	90	75	*13*
9	*9*	30	50	*15*	60	60	*12*
10	*8*	60	30	*13*	90	35	*13*
11	*17*	80	60	*12*	160	50	*12*
12	*24*	30	25	*24*	60	35	*24*
13	*17*	32	25	*15*	50	50	*12*
14 a	*15*	70	40	*11*	110	65	*12*
14 b	*10*	45	40	*12*	60	60	*5*
15	*6*	85	35	*5*	150	55	*4*
16	*3*	30	35	*3*	50	40	*3*
17	*7*	35	50	*7*	50	50	*6*
18	*6*	60	25	*10*	100	40	*10*

For example in experiment No. 1 the frequency was 20 cycles/min after 34 minutes when the pressure was 30 mm Hg and later (70 minutes after occlusion) with a pressure of 50 mm Hg the frequency was 15 cycles/min. Experiment No. 14 *b* was carried out on the same ureter as 14 *a* and was begun 15 minutes after the conclusion of 14 *a*.

large pressure amplitudes during and after every action potential are seen. At high pressures these pressure waves are reduced and disappear while the action potentials remain (Figs. 7 *b* and *c*); at the same time contractions can be seen clearly in the diameter recording.

Fig. 8 shows the contractility in conditions of free communication between the pelvis and ureter, and the oscillations synchronous with the arterial pulse. The diameter variations in

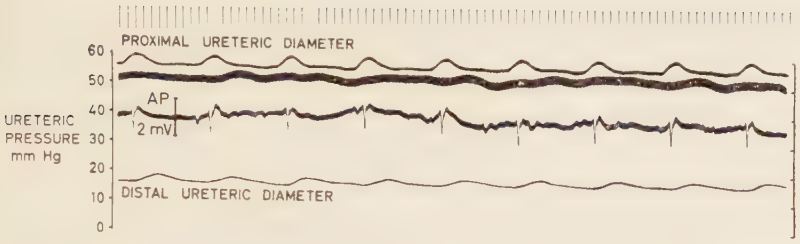


Fig. 9. Forward moving peristalsis with a ureteric pressure of 50 mm Hg. (Pelviureteric connections intact.) The ureteric pressure curve shows slow waves due to respiration with superimposed, very small oscillations synchronous with the arterial pulse. The electromyogram was recorded from the same level as was the distal ureteric diameter. The course of events is as follows (from left to right): First a proximal ureteric contraction is seen, followed by an action potential (distal), preceding the distal contraction. A few seconds later a second proximal contraction takes place and the chain of events is repeated etc. Uppermost, time marking in seconds. Recorded with Visicorder.

Fig. 8 are rather unclear due to the low sensitivity of the recording system used. The diameter recordings were therefore displayed simultaneously on a cathode-ray oscilloscope with high amplification, and distinct contractions were observed. During the recording of Fig. 8 *b* a respiration artifact unfortunately appeared, so that one ureteric contraction was completely obliterated.

The relationship between the action potentials and contractions may also be seen in Figs. 9 and 10 *b*, which were recorded under conditions similar to those in Fig. 8.

The frequency showed a tendency to decrease on continued increase in pressure or on prolonged stasis (at the same pressure). The difference was small, however, in several cases. *The highest pressure reached was 75 mm Hg, and ureteric activity was still retained at this level*, the frequency being 13 contractions per minute and the period of total occlusion 90 minutes. A summary of the data regarding frequencies, ureteric pressure and occlusion periods may be seen in Table 1.

The duration of the individual contractions varied between 2 and 5 seconds. The amplitude of the action potential was as a rule 1–2 mV with extreme values of 0.5 and 4 mV and a duration between 0.25 and 0.60 seconds (Figs. 13 *c*, 14 *b* and 16 *c*, chapter V). The latent period between the beginning of the action potential and that of the ureteric contraction (measured as incipient

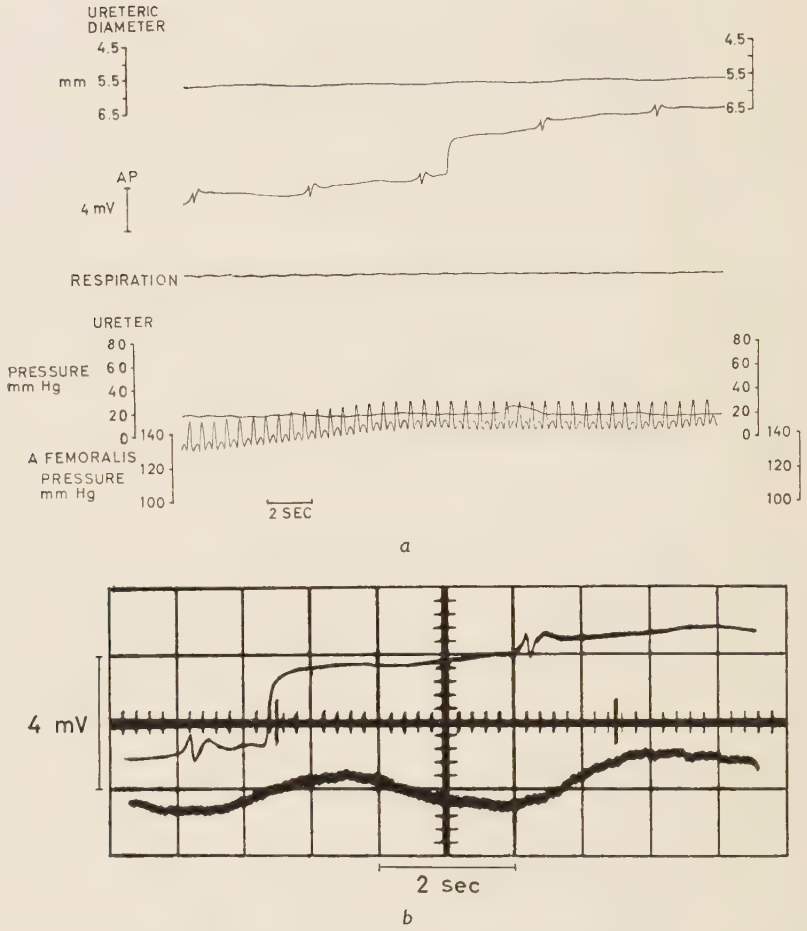


Fig. 10. Ureteric activity four minutes after Celocurin administration. (Pelviureteric connections intact.) There are regular ureteric contractions but no pressure increase. (Fig. 10*a* Optical oscillograph.) In Fig. 10*b* the third and fourth contractions with their preceding action potentials (above) are illustrated with the cathode ray oscilloscope traces in order to demonstrate more clearly the variations in ureteric diameter (lower curve).

diameter reduction) was 0.4–0.5 seconds. The latent period showed a tendency to increase in prolonged experiments, where the action potential also tended to decrease in amplitude and change in form.

In several cases there was no difficulty in observing visually the downwardly propagated peristaltic waves, in spite of high

intraureteric pressures. There was good correlation between the passage of a visibly propagated peristaltic wave past the electrode site and the appearance of an action potential. In the two cases where two diameter indicators were used, a contraction was constantly recorded at the proximal indicator before the action potential and contraction at the distal indicator (Fig. 9). A similar sequence of the contractions was observed in a few experiments of similar type in which three diameter indicators and no action potential recording were used.

In all cases where Celocurin was used, the dog was allowed to breathe pure oxygen for 20–30 minutes before the Celocurin was administered, and in this way no respiratory assistance was required during the few minutes immediately following the commencement of paresis (apnoeic oxygenation). Recordings were made when all striated muscle activity including respiratory movement had ceased. In all cases except one the ureter remained entirely unaffected, and no alteration occurred in the frequency, pressure or electromyogram. Fig. 10 shows the ureteric activity after the commencement of apnoea. The diameter variations on the oscillograph recording (Fig. 10 *a*) are small, and appear more clearly in the oscilloscope picture (Fig. 10 *b*). In one case there was a pronounced rise in arterial pressure (vasoconstriction?) following the Celocurin administration, and the ureteric pressure decreased simultaneously. When the ureteric pressure dropped below 25 mm Hg, distinct pressure variations due to contractions occurred.

No relationship between the respiratory movements or the abdominal pressure variations due to them and the ureteric activity was found, apart from mechanical artifacts. Nor was there any relationship between the arterial pressure variations and the ureteric activity.

Discussion

Electromyography at high intraureteric pressures

Electroureterograms have been used by several previous workers as a means of studying ureteric function. Intraluminal electrodes have been used most frequently (Hanley 1953, Franksson and Petersén 1953, Calafati *et al.* 1954, Sleator and

Butcher 1955, Butcher and Sleator 1955, Butcher and Sleator 1956, Corey *et al.* 1956, Butcher *et al.* 1957, and Weinberg and Siebens 1958), while in a few investigations electrodes have been applied to the adventitia (Orbeli and v. Brücke 1910, Weinberg and Hoffman 1961, Weinberg 1962) or inserted intramuscularly (Baker and Huffer 1953, Garg *et al.* 1959, Shiratori *et al.* 1959, Shiratori and Kinoshita 1961 *a* and *b*, Shiratori and Chiba 1961). An intraluminal electrode technique is very liable to artifacts, since good contact with the ureteric epithelium should be maintained, and at the same time distension by a catheter that is too large must be avoided. The different types of extraluminal electrodes give more exact information about the action potentials and are thus to be preferred. It is true that an intramuscular electrode damages the ureteric tissue locally, but the recording is made the whole time from a well-defined static point, in contrast to juxta adventitial electrodes over which the ureter is able to slide.

The present technique is very similar to that used by Shiratori and his collaborators, and appears to give almost identical results in dogs with respect to the form, amplitude and duration of the action potentials. Shiratori described three types of waves with amplitudes varying between 0.5 and 1.5 mV and durations of 0.2–0.4 seconds. Baker and Huffer (1953) used another technique. A needle (hypodermic needle No. 28) was used as an active electrode, and the indifferent electrode was placed in the skin of the abdomen. The action potentials obtained in this way had an amplitude of about 0.2 mV, thus lower than those found by Shiratori. The duration was also shorter, i.e. about 0.1 second. The different results appear to be due to differences in the method of recording. Under good conditions action potentials similar to those of Shiratori are obtained with an intraluminal technique (Sleator and Butcher 1955) and with adventitial electrodes (Weinberg and Hoffman 1961).

The two most common types of action potentials in the Japanese material were also most common in the present investigation, while the third form of wave (Fig. 14 *b*), which has the lowest amplitude and was observed by Shiratori and collaborators especially in conditions when the peristalsis was weak, occurred most often with high pressures or in prolonged occlusion experiments.

The form of the action potentials thus seems to vary with the condition of the muscle cells, but the recording of electromyograms does not *per se* necessarily involve serious reduction in function. The most prolonged experiment in this material extended over 150 minutes, while Shiratori stated that is was possible to obtain the spikes unchanged in appearance for three hours. The position of the electrode in the ureteric wall seems to be an essential factor as regards the appearance of the action potentials. Electromyograms with different types of electrodes give fairly divergent results, and it is reasonable to suppose that a varying intramural electrode position might give variations in the form of the action potentials. The appearance of the individual spike is therefore probably less important than the fact of its existence. The occurrence of potential variations alone is not, however, necessarily evidence of ureteric contractility. It only indicates that localized depolarizations (or very local non-propagated contractions) occur in the smooth muscle, but whether regular contractions arise can only be determined by some form of simultaneous diameter indication. *If both an action potential and a subsequent decrease in diameter are recorded, this must be regarded as proof that a contraction has taken place.* The experiments showed that even when the intraureteric pressure rose to a height such that the amplitude of the contraction-dependent pressure variations decreased and finally ceased because of damping, the contractions remained. *The most usual way of identifying the ureteric activity, i.e. the measurement of ureteric pressure changes alone, must thus be regarded as inadequate at such intraureteric pressure levels when there is open communication with the renal pelvis and the damping effect of the latter influences the observed pressure changes.*

Roentgen contrast investigations of the ureter (Benjamin *et al.* 1956) also appear to be unreliable when a certain degree of distension has been exceeded. This is to be expected, since with high pressure and pronounced dilatation the lumen of the ureter is not completely closed during contraction (Graves and Davidoff 1923). It is probably quite difficult to identify on a roentgenogram partial decreases in diameter on ureteric contractions. On the other hand the contractions can be observed when the degree of dilatation is more moderate. Benjamin *et al.* (1956) demon-

strated ureteric contractions with cinefluorography in obstructed dog ureters in the presence of moderate dilatation.

The effect of intravenous NaCl infusions on the ureteric pressure

As shown in chapter II ureteric activity can be demonstrated in perfusion experiments at high hydrostatic pressure levels. In experiments with intact pelviureteric communications the ureteric pressure seldom rises spontaneously above 45 mm Hg. After a more or less rapid pressure increase, the pressure required to dilate the ureter and establish free communication between the ureter and pelvis is reached. In addition, if the diuresis is sufficient, the pressure increases further to a level which should correspond approximately to the filtration pressure in the glomeruli. The "pattern of free communication" which is shown in these cases by the ureteric pressure recording completely reflects the changes in arterial pressure. With every pulse beat the pressure rises and falls to some degree, and slow arterial pressure oscillations and variations in the arterial pressure synchronous with respiration are very well reflected. These phenomena have been described by several authors (Risholm *et al.* 1959, Taylor and Ullman 1961, Kiil and Aukland 1961 *b*, Boyarsky and Martinez 1962, and others). Because of the stasis in the ureter the kidney is affected by the increased pelvic pressure, and the diuresis decreases (Selkurt *et al.* 1952, Kiil and Aukland 1961 *b*). If a diuretic is given the pressure can be forced higher than 45–50 mm Hg even without change in the arterial blood pressure. Taylor and Ullman obtained maximal pressures of 148 mm Hg after intravenous injections of 23% mannitol in normal saline. If infusions of isotonic NaCl are repeated in moderate amounts the ureteric pressure increases sharply within $^1/_2$–1 minute after each infusion, and can be raised to 100 mm Hg without difficulty. It seems to be predominantly a local intrarenal reaction that causes the high pressures after the administration of normal NaCl. Infusions of hypotonic NaCl also probably have this effect. Kiil and Aukland (1961 *a*) gave 0.45% NaCl intravenously in quantities of 4–8 ml/min and obtained maximal pelvic pressures of 134 cm water. If the diuresis was maintained with repeated infusion of 5% glucose the pelvic pressure increased, but not in sharp steps, or if a fluid with hypernormal colloid

osmotic pressure but containing no electrolytes is administered (10% Dextran) a transient reduction of the pelvic pressure is obtained (Bäcklund and Nordgren, to be published). Since it is improbable that pressures above 100 mm Hg occur in the urinary tract, either physiologically or under pathological conditions, it has not been considered worthwhile to attempt to reach such pressure levels experimentally. The study of the ureteric activity has therefore been mainly confined to the pressure region of 30–60 mm Hg.

Ureteric peristalsis at high intraluminal pressures

Only the lower part of the ureter was studied. In the majority of the experiments the ureteric diameter was only measured at one place, and it is possible that the activity which was observed was local to the distal ureter and therefore simulated peristalsis. As mentioned in chapter II, it has been claimed that the power of contraction ceases last in the lower third. *In several experiments, however, a fully visible peristaltic wave was observed, and in the cases where several diameter indicators were used a distal contraction was preceded by a proximal one* (Fig. 9). Antiperistalsis was not demonstrated with certainty in this series of experiments, but it probably occurred. It has been observed, among others, by Trattner (1932), Sleator and Butcher (1955) and Melick *et al.* (1962). The latter studied human ureters. On the other hand Shiratori and Kinoshita (1961 *a*) did not observe any antiperistaltic discharges in normal dog ureters.

The fluid transport along an occluded ureter does not cease even if there is total distal occlusion. The continually persistent contractions produce a circulation of fluid within the closed system. Furthermore, return transport from the renal pelvis to the blood can take place (Risholm and Öbrink 1958), apparently predominantly via the lymphatics (Földi *et al.* 1959).

The effects of the experimental procedure

Of especial interest is the contraction frequency in the occluded ureter. A slowly decreasing frequency was found when the pressure was high and/or the occlusion was maintained for a long period. This was probably a result of the experimental procedure. At the same time a decrease in the amplitude of the potentials

was seen in a number of cases, and also sometimes a protraction of the latent period between the action potential and the commencement of contraction. The latent period was considerably longer than that described by Sleator and Butcher (1955). Using another technique, in which the electrical and mechanical activity were not measured at the same place, they calculated a latent period of 0.1 second from the action potential to the beginning of mechanical activity. In the present investigation, however, the ureter was not in its natural milieu. Both cooling and drying may contribute to a tendency to a slower reaction, and such effects are additive to the effect exerted by operation trauma and increase in pressure. The anaesthetic used, on the other hand, probably exerted no untoward effect on the ureter. Care was taken to produce an adequate depth of anaesthesia. Too light an anaesthesia can lead to profuse recording artifacts, a phenomenon which has also been described by Baker and Huffer (1953). These authors studied the electromyogram from dog ureters under anaesthesia with ether or intravenous sodium seconal, and also the importance of anaesthetic depth. No effect on the electromyogram was shown in any of the cases studied.

The durations of the individual contractions varied, but the range was similar to that found by Boyarsky and Martinez (1962). With low diastolic pressures they recorded a systolic duration of 2–5 seconds, and in studies on man Bors and Blinn (1955) found a variation of the ureteric systole of between 1.5 and 4 seconds.

In spite of the unfavourable external conditions the ureters were able to contract for long periods at high intraluminal pressures. No definite conclusions can be drawn, however, regarding the length of time that an occluded ureter is able to maintain peristalsis, but a period of several hours seems a reasonable minimum estimate. In a series of experiments with partially obstructed and dilated dog ureters Baker and Huffer (1953) found only small electromyographic changes after 2–4 months. The peristalsis was reported as being forceful with a normal rate, but the intraureteric pressure was not determined. No great degree of muscular atrophy occurs in chronically obstructed ureters; there is predominantly an increase in the amount of fibrous tissue (Stein and Weinberg 1962). It has also been

observed that the ureteric muscles can hypertrophy, proximally to a ureteric stone (Wildbolz 1952), and after partial ureteric occlusion with dilatation (Benjamin *et al.* 1956).

Pacemakers in the ureter

The existence of a pacemaker for ureteric peristalsis has been discussed, and Narath (1951) and Morales *et al.* (1952), among others, held the view that the contraction waves began in the calyces and were propagated to the ureter via the renal pelvis. Sleator and Butcher (1955) also described this finding, but considered it hazardous to conclude from their results that a renal pacemaker normally exists. Bozler (1942), on the other hand, found in the extreme renal end of isolated ureters a small region with high spontaneous activity, from which the propagated ureteric contractions arose. Bozler regarded this as a pacemaker situated at the pelviureteric junction. It was not the intention in the present investigation, however, to determine from what part of the urinary tract the propagated ureteric contractions usually originate, but to study whether the respiratory movements or changes in the arterial pressure can constitute a trigger mechanism. In a few cases the frequencies of respiration and peristalsis coincided, but no definite relationship was found. Pfeifer (1949), with roentgen contrast investigations of the renal pelvis, found good correlation between the respiratory movements and the filling variations of the renal pelvis. According to Pfeifer deep inspiration could provoke a peristaltic wave. If this occurs it is probably only an occasional coincidental occurrence. One of the aims of the experiments with Celocurin was to eliminate any possible respiratory stimulation of the ureter; in no case did total respiratory paresis result in any change in the ureteric activity. Nor did Celocurin affect the electromyogram. The same results were also obtained by Shiratori and Chiba (1961) who after the administration of succinylcholine chloride in doses of 1 mg/kg body weight found no change in the electromyogram from dog ureters.

The part played by the arterial pressure in ureteric peristalsis is indirect. It may be considered to be a "supply pressure" for diuresis and also determines the appearance of the communication pattern. If the effect of the arterial pressure on the kidney

is decreased by vasoconstrictors or by compressing the renal artery the pressure falls abruptly in the pelviureteric system and contraction-dependent pressure waves are seen, probably as an expression of the fact that free fluid communication between the pelvis and ureter has been interrupted in some way (Bäcklund and Nordgren, to be published). With the exception of these effects the arterial pressure does not appear to influence the ureter, and no relationship has been shown between the contraction frequency and the variations in arterial pressure.

CHAPTER IV

Ureteric diameter variations and electromyograms at low intraluminal pressure levels

A number of studies of ureteric peristalsis at low and moderate intraureteric pressures have been reported in the literature. In recent years electromyography, most frequently with intraluminal electrodes, and with simultaneous pressure recording without occlusion of the ureter, has been used to study the point of origin and the rate of propagation and also the importance of the rate of flow. Both roentgenograms and intraluminal detectors sensitive to diametric changes have been used to study ureteric contractions. A combination of pressure measurements, diameter recordings and electromyography does not appear to have been utilized, however, for the analysis of ureteric function at physiological pressure levels. In order, therefore, to study more closely the local electrical and mechanical events accompanying the passage of a peristaltic wave, a series of experiments with measurement of the intraureteric pressure and simultaneous recording of electroureterograms and diameter changes has been performed.

Material and methods

Nineteen adult dogs of both sexes and weighing between 8.5 and 33 kg were used for the experiments. The same operative technique was used as described in chapter III. In those cases, however, where several diameter indicators were used, a larger portion of the ureter was freed in order to ensure the best conditions for the indicators placed at the selected site. A ureter which has been inadequately dissected out cannot move freely and the diameter recording is then made considerably more difficult.

The ureters were cannulated in the same way and with the same types of catheter as described in chapter III. The ureteric pressure, arterial pressure and respiration were also recorded with

the same methods as before. Intravenous injections of 0.9 % sodium chloride solutions were given as a diuretic when required.

Altogether twenty-two experiments were performed, and in fourteen a single indicator of the type described in chapter III was used for diameter recordings. In two experiments two indicators placed 25 mm and 30 mm apart, respectively, were used, and in the remaining six experiments three indicators were used; the distance between the proximal and intermediate indicators was 15–23 mm, and between the intermediate and the distal 16–38 mm. The distance between the tip of the ureteric catheter and the distal diameter indicator varied between 5 and 25 mm. The greatest distance, measured from the tip of the catheter to the most proximally placed indicator, was 75 mm.

For recordings of the electromyogram an electrode was inserted into the wall of the ureter between the claws of the most distal diameter indicator. In a few cases, however, the electrode was placed somewhat proximally or distally to this level. A silver electrode was used in ten cases and a platinum electrode in the remaining twelve. The electrodes were constructed as described in chapter III. The electromyogram was also recorded as described in the previous chapter.

In ten experiments the optic oscillograph described in chapter II was used for recording, and in the remainder a Visicorder 906 A-1 with D.C. amplifiers (Grass Low Level Preamplifiers) for the ureteric pressure and diameter detectors. The experiments were performed in such a way that before the recordings from a ureter were commenced, the urine was allowed to run freely from the ureteric catheter. During this time the diuresis was estimated roughly, and the action potentials and diameter variations were assessed. The ureteric catheter was then connected to a pressure transducer (Elema EMT 472 a), no urine being allowed to escape from the ureter. An attempt was made to obtain moderate pressure levels (5–20 mm Hg) so that the relationship between the action potentials, ureteric contractions and pressure rises could be studied.

Results

There were certain constantly recurring difficulties. Careful preparation was required to obtain good electromyographic re-

cordings and at the same time satisfactory diameter measurements from two or three levels. It was sometimes impossible to complete an experiment without making slight adjustments of the ureteric position in the indicator claws. As in the investigations described in chapter III the placing of an electrode in the ureteric wall at the site of an indicator resulted in a local decrease of movement. In control experiments, when the electrode was removed, the diameter variations increased. In spite of the presence of the electrode, however, the deflections were usually sufficiently large for the diameter change to be identified with certainty.

The form, amplitude and duration of the action potentials were the same as described in chapter III. The range of variation of these parameters as recorded was large, and by changing the position of the electrode in cases where the potentials were small, a considerably higher amplitude was often obtained.

Pressure variations. The occurrence of diphasic pressure waves with peristalsis

The pressure waves were of two principal types. Either a single pressure wave occurred after each action potential or, as in the vast majority of cases, there was a pair of pressure waves. In the latter case the first wave was as a rule of lower amplitude and shorter duration than the second wave (Fig. 11). The interval between the waves varied considerably, and was sometimes so great that they appeared entirely separate. In other cases the interval was so small that the waves were almost confluent. In some cases the first wave had a greater amplitude than the second, but it was never of longer duration. The action potential belonging to the wave complex always appeared during the first wave. Its precise localization could vary, but it was never earlier than the beginning of the first wave. In some cases a triphasic pressure wave complex appeared. To judge from wave form and time relationship to the action potential the first of these three waves was an extra wave, while the next two corresponded to the ordinary diphasic complex. Thus the action potential occurred at the same time as the second wave of the triphasic complex.

These different types of peristaltic waves were not unique for this experimental series, but were observed in all the present

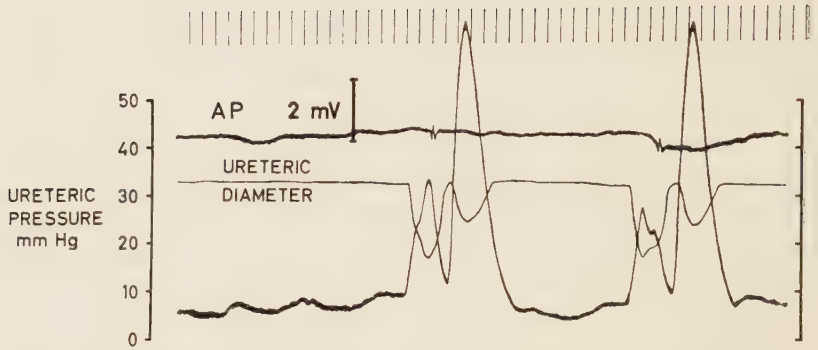


Fig. 11. The diphasic pressure wave associated with peristalsis in a ureter with its connection to the pelvis intact. During the first smaller pressure peak there occurs an action potential and at the same time (at the distal site of measurement) the ureteric diameter is increased (down going deflection). The second pressure peak is due to contraction at and distal to the level at which the electrode is situated. In spite of the muscular contraction the ureter dilates appreciably even simultaneously with the maximum of the second pressure peak. This is a result of the obstruction in outflow. Uppermost, time marking in seconds. Recorded with a Visicorder. (The picture is the same as Fig. 7*a*.)

ureteric studies when a recorder with a sufficiently fast paper speed was used.

With increasing ureteric pressure the amplitude of the pressure waves decreased independently of whether they appeared single or in pairs. As a rule the first wave of a pair disappeared before free fluid communication between the ureter and pelvis was established.

Diameter variations during the passage of the peristaltic waves

Ureteric diameter recordings showed different patterns depending on the type of peristaltic wave and also on the intraureteric pressure.

At pressures up to about 10 mm Hg the ureteric diameter was so little increased during inactivity compared with the collapsed resting state at zero pressure that a contraction was unable to produce any measurable diminution in diameter. In the distal ureter the fluid already present inhibited compression and thus the contraction occurring was almost isometric. It was therefore very usual that the ureter became somewhat dilated during a contraction at the distal measuring point. At higher pressures

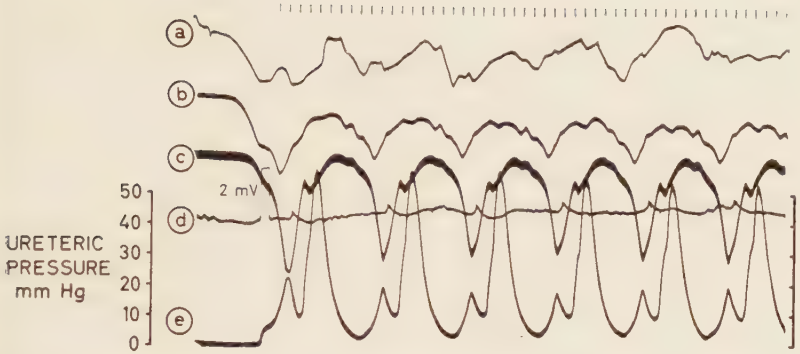


Fig. 12. Regular contractions in a ureter with intact pelviuretic connections. *Recording with three diameter indicators at different sites;* (*a*) proximal, (*b*) somewhat more distal, (*c*) at the electrode level. (*d*) is the electromyogram and (*e*) the intraureteric pressure. Note the successive dilatation phases in *a*, *b* and *c*. An action potential and a small pressure rise occur simultaneously with the dilatation at (*c*). Uppermost, time in seconds. Recorded with a Visicorder.

the ureter became more and more dilated and the contractions became more clearly manifest.

In peristalsis with biphasic pressure waves the first wave coincided with a marked dilatation of the ureter, during which period the action potential also occurred (Fig. 11). Only exceptionally was this dilatation so small that it could not be identified with certainty. Dilatations were also observed when the ureter was not occluded, and there was no obstruction to emptying. The second, longer pressure wave occurred together with a significantly smaller dilatation (at low pressures) or with a contraction (at higher pressures).

The propagation could be studied when two or three diameter indicators were used. The propagated change consisted first of a larger dilatation, followed immediately by a smaller dilatation or a diminution of the ureteric diameter (Fig. 12). As a rule the first pressure wave (pressure measured at the distal end of the ureter) in the diphasic curves coincided with the diminution at the upper or middle diameter indicators (see Fig. 14 *a*, chapter V).

When the basal pressure was increased the dilatation, in parallel with the first wave, disappeared, while the action potential remained unaffected.

In those cases where the peristalsis was accompanied by only a

single pressure wave, it was nevertheless observed that a dilatation of the ureter preceded the pressure wave, the action potential occurring with the dilatation. With low pressures there was also an additional but much smaller dilatation which occurred at the same time as the pressure rise.

Only in exceptional cases were neither ureteric dilatation nor a pressure rise observed at the time of the action potential.

Velocity of propagation and frequency of contraction

The velocity of propagation in the ureter was determined in the eight experiments where two or three diameter indicators were used. In all cases the velocity was constant in a particular experiment and in different experiments varied between 12 mm and 20 mm per second. The distance between which the measurements were made varied between 25 mm and 75 mm.

The use of more than one diameter indicator made it possible to determine the contraction frequency in different parts of the ureter. It was a common finding in at least some part of an experiment that the, or those, indicators which were placed proximal to the electrode showed a frequency double that of the action potential recording. The difference could also occur between the proximal and intermediate indicators while thus the latter and the distal indicators had the same frequency. The frequency change sometimes occurred very suddenly and was of relatively short duration. In a few recordings the frequency in the distal segment was only $^1\,_3$–$^1/_4$ of that in the proximal part. These frequency differences were not associated with any particular pressure level.

The occurrence of antiperistalsis was also studied. Retrograde peristaltic waves were unusual but they did sometimes occur. As a rule they were occasional waves which turned at the ureteric catheter and then went backwards.

The action potential frequency was observed in some experiments to alter so that when the pressure rose to 10–20 mm Hg the spikes appeared not only before the pressure waves but also in their terminations and without a further pressure rise. Another type of arrhythmia was the appearance of spikes in pairs shortly before a contraction. This variation was unusual and occurred at higher intraureteric pressures.

Discussion

Diameter variations in contraction of the ureter

A peristaltic contraction wave in the ureter as a rule means a wave of contraction of the ureteric musculature propagated from the pelvis down to the urinary bladder. The circular musculature in contracting produces mainly a narrowing of the ureteric lumen, while contraction in the longitudinal muscles produces a shortening of the ureter but probably not a complete occlusion of the lumen. According to Satani (1919 *c*) there are in the ureteric wall an outer and an inner layer of longitudinal musculature and an intermediate layer of circular muscles. The circular muscles predominate in the middle third of the ureter and while diminishing in the distal third are nevertheless present right down to the entrance in the bladder wall.

The anatomical distribution of the circular and longitudinal muscles in different regions of the ureter produces variations in the forces available for the compression of the lumen and thus it is probable that the ability to propagate the ureteric contents also varies from place to place. With such a situation there may be a tendency for the formation of pools in certain parts of the ureter. At least with low intraureteric pressures the lumen is pressed together completely with ureteric contraction and the ureteric contents are pressed as a bolus in a distal direction. Since, however, the ureteric lumen in rest is entirely collapsed, the downward displacement of a bolus must mean that the ureteric walls are forced apart and thus a local intraluminal pressure rise must occur. Melick *et al.* (1962) have by cinefluorography and simultaneous pressure measurement followed the passage of boluses in human ureters. They observed that the ureteric walls both above and below the bolus were completely collapsed and that a pressure rise could be recorded only where the walls were distended by the bolus. The cinefluorographic technique was also used by Benjamin *et al.* (1956) and Swenson *et al.* (1959), who also found that the ureteric lumen was completely compressed during contraction. Benjamin *et al.* stated that after contraction the lumen was opened again by the next contrast injection arriving from above. The dilatation of the ureter that occurs in front of a contraction wave has been described earlier (Protopo-

POW 1897, ORBELI and v. BRÜCKE 1910, ANDERSON 1951, and others), and has been of importance in the theory that the ureter functions as a suction pump (LUCAS 1908, SLEATOR and BUTCHER 1955).

If the ureteric diameter is measured continuously the passage of the bolus should be recorded as a dilatation, and when the ureteric contraction passes the measuring point the lumen is again obliterated and the diameter regains the resting dimension, with the assumption that the entire ureteric content can be emptied distally. This is exactly the situation which was found in the experiments with the diameter indicators placed proximal to the electrode and at such a level that allowed a urine bolus to be pushed past in its entirety.

The conditions are different if the ureter is in stasis at a measuring point (e.g. distally near the catheter). When a contraction wave arrives, the bolus cannot be pushed on further and the ureteric lumen cannot be collapsed again completely. It must therefore be expected that after the initial dilatation there is a reduction in diameter, corresponding to the contraction, which cannot become total or subtotal before the muscular contraction in the ureteric segment immediately above has subsided sufficiently to allow the urine to be pressed backwards. When the ureter is slowly filled through diuresis an increasingly great part of the distal ureter becomes unable to obliterate the lumen completely. In this way free fluid communication through the whole of this part is obtained, and when a muscular contraction occurs in the distal part the fluid column can be pushed backwards through this dilated region to a part of the ureter since no ureteric occlusion hinders its passage. Contraction of the ureteric musculature distally should then be manifested as a small but distinct diameter reduction as compared with the value between contractions. This also occurred at pressures of about 10–20 mm Hg. At the same time the initial dilatation phase became smaller and disappeared. This also seems reasonable since it is difficult to believe that an observable bolus can be pushed into the dilated and fluid-filled ureteric tube. Thus the effect of muscular contraction in this region should be manifest only as a pressure rise, probably small and damped. Nevertheless it is possible that there was a small dilatation although none was

recorded. This might be due to the low sensitivity of the indicators. Van Citters (1960) was able to show in model experiments that in a fluid-filled elastic tube of the dimension of the aorta the front of a pulse wave is associated with a dilatation of the walls of the tube. The ureteric contractions were, however, propagated and possible mechanisms to explain this will be discussed below.

Pressure variations with ureteric contraction

As mentioned above, on the passage of a urine bolus into an empty ureter a certain intraluminal rise in pressure should occur when the ureteric walls dilate. This event corresponds to the course in the diphasic peristaltic wave pattern, which constituted the most common finding in the investigation. When the stream of urine is injected downwards into an empty ureteric segment the bolus jet should give a rapid moderate rise in pressure (bolus jet wave), varying with the power causing it and being succeeded by a more pronounced pressure wave when the contraction arrives at the tip of the ureteric catheter. A bolus jet can probably be very forceful. In experiments with exteriorized bladders Morales *et al.* (1952) observed that the urine could spurt more than 30 cm high from the ureter.

The latent period between a bolus jet wave and a "pressure wave" (rise in pressure due to contraction at the same level) probably varies with the excitability of the smooth musculature, the velocity of the bolus propagation and the ability of the ureter to dilate rapidly on intraluminal pressure increases (i.e. volume-pressure relationship). The fact that the mutual relationships between a bolus jet wave and a pressure wave showed such great differences can be explained by differences in anatomic structure, predominance of circular or longitudinal musculature, possible tissue damage or other factors. In some cases there was no bolus jet wave, and in these conditions the monophasic peristaltic pattern appeared. Since as a rule, however, there was an initial dilatation, the monophasic pattern appears to be only an extreme variant of the normal diphasic pattern. Diphasic and triphasic waves were recorded together with single waves by Rattner *et al.* (1957) in man. They obtained diphasic waves in all parts of the ureter. Small pressure rises preceding the contractions were also

described in man by KIEL (1957), who used pressure measurement catheters which did not obstruct the urinary flow.

When the ureteric pressure rises the bolus jet wave would also, as is the case with the dilatation phase, be expected to disappear. This was found to be so, and similarly, the pressure wave itself also disappeared gradually. This phenomenon has already been discussed in chapter III and will therefore not be discussed further here.

The occurrence of the action potential during the dilatation phase and bolus jet wave at lower pressures was constant. *It is thus only on occasions with increased tension in the smooth muscles (as a rule due to increased intraluminal pressure) that a spike appears and a contraction is provoked.* In certain experiments where the frequency was higher at a proximal than at a distal measuring point, stronger dilatations and or greater bolus jet waves were seen when the contraction was provoked distally than in those cases in which the lowermost segment remained inactive (see Fig. 13 *a*, chapter V). *This seems to indicate that the smooth muscle cell need to be stimulated with a certain minimal degree of extension if they are to respond with contraction.*

Arrhythmias in the peristalsis

Different forms of arrhythmia were observed. The fact that the frequency was sometimes higher in the proximal region has already been mentioned. Another additional possible reason for this is that when the ureteric content is pressed backwards by a distal contraction, this produces by extension of the ureteric wall a new peristaltic wave that is able to continue forwards until it encounters a refractory region. The refractory period for the ureteric musculature has been stated by PROSSER *et al.* (1955) to be 1–3 seconds and by ICHIKAWA and IKEDA (1960) as 1.5 seconds. It is possible that this period may be longer in a region that has been damaged by experimental preparations and the electrode puncture. Cooling of the ureter may also have similar effects. Reasons such as these do not explain, however, why for example frequency ratios, between two indicators, could suddenly change to 2: 1, 3: 1 or 4: 1. If these integral frequency ratios were due to antiperistaltic waves provoked from the distal part, it would be possible to determine this by the time sequence

of the diameter measurements. Such a sequence was never definitely observed, but cannot be excluded, since electromyographic information from a proximal site is also required to establish it. Spontaneously higher activity in the uppermost part of the ureter has been described, however, by several authors (Bozler 1942, Gould *et al.* 1955 *b*), and could play some role, at least in part, in the varying frequency. The ability of different ureteric segments to contract completely independently of one another, observed by Trattner (1932), may constitute yet another factor.

The action potentials exhibited another form of arrhythmia; with high pressures, in certain cases they appeared either in pairs before a contraction, or an extra action potential appeared at the end of a prolonged pressure wave before the basal pressure had been regained. It is probable in both cases that the prevailing tension in the ureteric wall produced extra depolarizations. On the whole at high intraureteric pressures the ureteric activity may be related to the continuous stimulation of the musculature provided by the internal tension. Whether propagation occurs because the ureter behaves as though it were a syncytium or is mechanically induced, either by means of extension in the neighbouring cell on contraction or provoked by a small local rise in pressure, will not be discussed here but will be treated in more detail in chapters V and VI.

The propagation velocity of the ureteric contractions

The propagation velocity in the ureteric musculature has been mainly investigated previously by electromyography. In dogs Shiratori *et al.* (1959) found a variation between 38 and 56 mm/sec, while Shiratori and Kinoshita (1960 *a*) reported higher velocities in the middle part of the ureter than in the remaining areas. According to these authors the distal propagation velocity of the peristaltic wave was between 21.4 and 29.7 mm/sec. They found velocities of 20–45 mm/sec in antiperistaltic waves which had arisen after division at the pelviureteric junction (1960 *b*). Prosser *et al.* (1955) found a velocity of 30–40 mm/sec in dog ureters, while Calafati *et al.* (1954) noted 20–30 mm/sec. Cooling and drying may be mentioned as possible explanations for the lower velocity in the present study. Baker and Huffer (1953) and Butcher *et al.* (1957) obtained a reduced velocity under

similar circumstances. Ichikawa and Ikeda (1960) also made similar observations on isolated guinea-pig ureters. They obtained a propagation velocity in the action potentials of 24.1 ± 9.1 mm/sec at 32°C. The peristaltic frequency probably also plays a part. Ichikawa and Ikeda and also Sleator and Butcher (1955) stated that the propagation velocity was lower if a stimulus reached the ureteric muscles during a relative refractory period.

That the velocity can vary between different parts of the ureter was also stated by Graves and Davidoff (1923). In rabbit ureters they found a contraction velocity of 18.3 mm/sec in the upper third, 15.4 in the middle third and 13.3 mm/sec in the lower third. Whether there was any definite difference in velocity in different parts of the ureter in the present material cannot be determined, since the diameter recording is not a sufficiently exact method for determining small differences.

CHAPTER V

The peristalsis in an anastomosed ureter

It was mentioned in chapter IV that peristaltic propagation in the ureter is possibly maintained by the excitation of distal muscle cells by means of extension or intraluminal pressure increase on contraction in the more proximal muscle cells. In order to study this problem more closely and to eliminate all myogenic, nervous or humoral influences coming from above, a series of experiments were performed in which the ureter was divided and re-anastomosed via a short catheter without direct contact between the two cut surfaces.

Material and methods

Thirteen adult dogs of both sexes weighing between 10 and 33 kg were used for the experiments. They were anaesthetized with intravenous injections of veterinary Nembutal® (Abbott) in doses of 30 mg/kg body weight. In prolonged experiments the Nembutal dose was repeated to retain an unchanged depth of anaesthesia.

The same operative technique was used as in the experiments described in chapter IV. Recordings of respiratory movements and the arterial blood pressure were made as described in chapter III. For cannulating the ureters the same type of polythene catheters were used as before. The tip of the catheter was inserted 5–10 mm proximally from an incision made near to the urinary bladder. Care was taken to minimize damage to the vascular supply of the ureter.

Altogether sixteen experiments were performed; in ten cases the ureteric peristalsis was also studied before division and re-anastomosis. These experiments are included among those described in chapter IV. In the remaining six experiments the ureters were divided straight away. The ureter was transected at a distance of 16–46 mm from the tip of the ureteric catheter,

and the blood vessels were ligated. A short polythene catheter, varying in length between 15 and 20 mm and with an external diameter suited to the lumen of the ureter, i.e. such that no distension or constriction should occur, was inserted with one end in each ureteric stump, and secured with ligatures. The sectioned surfaces were not allowed to touch one another, but were isolated by a piece of rubber which had been threaded on to the anastomosis catheter before insertion. Two diameter indicators of the type previously described were placed proximally to the anastomosis, the distance between them varying between 9 and 25 mm and that between the more distal indicator and the anastomosis varying between 10 and 21 mm. A platinum electrode (see page 25) was inserted intramurally into the distal ureteric stump 6–24 mm from the anastomosis, and a third diameter indicator was placed at the same level or very close to it. The technique for the recording of electromyograms was the same as described in chapter III. In some of the cases in which the peristalsis was studied before division, it was possible to perform the anastomosis without displacing the electrode or the diameter indicators. The recordings before and after anastomosis were therefore made from exactly the same levels. In one case only two diameter indicators were used, one being placed proximally to the anastomosis and the other distally at the site of the electrode.

The aim of the experiments was to study the peristalsis after total occlusion of the ureters, in particular at intraureteric pressure levels between 0 and 20 mm Hg. When the diuresis was poor with an insignificant or absent pressure rise after ureteric occlusion, intravenous injections of 0.9% sodium chloride solution were administered to increase diuresis.

For simultaneous intermittent recordings of ureteric diameters, pressure and electromyograms a Visicorder type 906 A-1 was used. The D.C. amplifiers used both for the diameter indicators and for the ureteric pressure transducer (Elema EMT 472 a) were Grass Low Level Preamplifiers. In between the periods when recordings were made with the Visicorder the electromyogram was followed continuously and the diameter changes in the distal ureteric stump intermittently on a two-channel oscilloscope. A polaroid camera was used for photographing the oscilloscope picture.

Results

The method used involved considerable difficulties with regard to the maintenance of a satisfactory blood supply to the distal ureteric stump. It was at times impossible not to damage the arterial blood supply, and in several cases ligation of the vessels on anastomosis sooner or later produced venous stasis in the distal stump, as evidenced by swelling and signs of increased stiffness of the walls. The period of observation in which conditions were favourable was thus in these cases relatively short (15–42 minutes) while in the remaining experiments the duration of the experiment could be extended to one hour or longer. In four experiments the peristalsis could be observed for two hours or more after anastomosis. In three cases the experiment could not be completed, either because of inactivity in the whole ureter, or because of technical failures.

Variations in pressure and diameter in anastomosed ureters

In altogether thirteen experiments satisfactory observation conditions were obtained, and peristalsis and contractility were observed in both ureteric stumps. In seven of the cases recordings were also made before the ureter was divided.

The pressure- and diameter variations in contraction waves were in principle the same as in the experiments described in chapter IV (p. 43). Thus as a rule a ureteric dilatation corresponding to a rapid, moderate pressure increase (bolus jet wave) was seen before each contraction, followed by a more protracted pressure wave. If the ureteric pressure did not exceed 10 mm Hg the ureteric diameter diminution corresponding to the contraction appeared to be rather weak or absent. The action potentials occurred during the dilatation phase at the passage of the bolus jet wave, and had the same appearance as described previously. In seven of the thirteen anastomosis experiments two or three bolus jet waves appeared in succession in the distal ureteric stump before its contraction. The bolus jet waves always occurred with dilatations distally. In the proximal segment they were synchronous at first with the dilatation at one or both

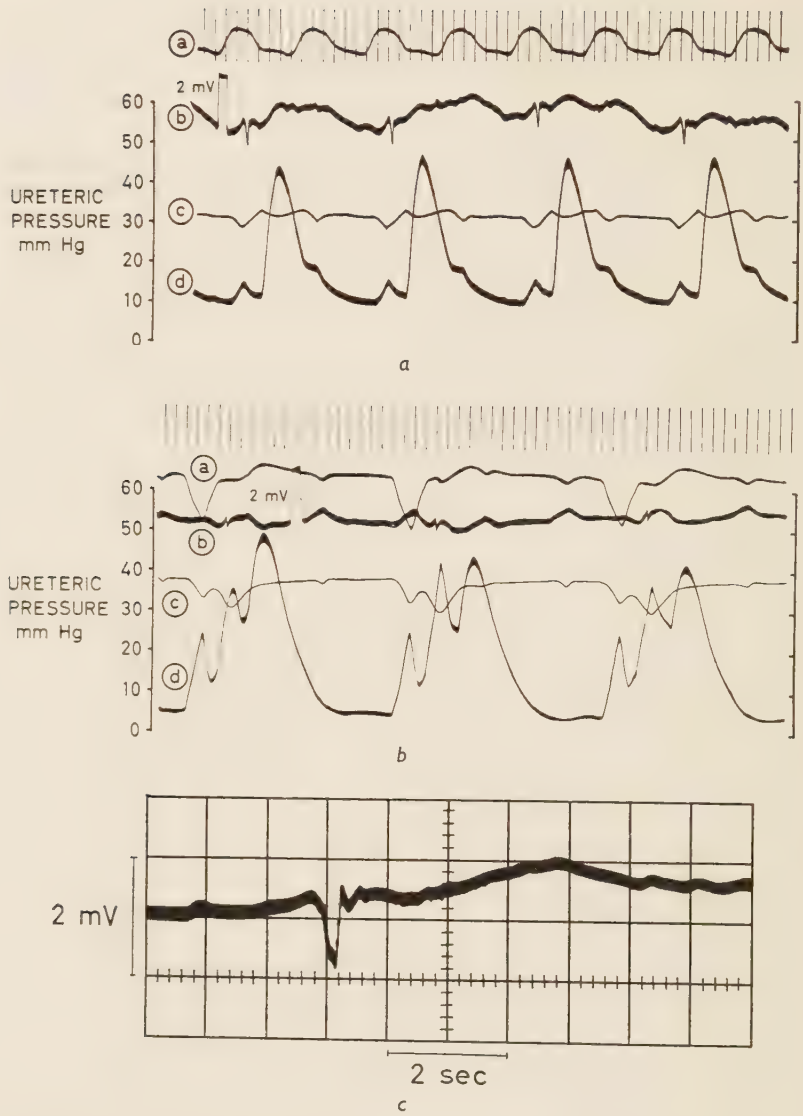


Fig. 13. Ureteric contractions before (13*a*) *and after* (13*b*) *transection and re-anastomosis.* In both figures time in seconds is indicated uppermost, and then the proximal ureteric diameter (*a*), electromyogram (*b*), distal ureteric diameter (*c*) and ureteric pressure (*d*). (*b*) and (*c*) were recorded at the same level. Note that in 13*a* each proximal contraction results in a distal dilatation and rise in pressure but only each alternate proximal contraction is followed by a distal contraction. In 13*b* the basal pressure in the ureter is lower and thus the contractions are not so marked. There are respiration artifacts in (*a*), (*b*) and (*c*) in Fig. 13*b*. Recorded with a Visicorder. Fig. 13*c* shows an action potential recorded with an oscilloscope somewhat later than 13*a*.

of the two diameter indicators; later they also came with the contraction somewhere in the proximal stump. The bolus jet thus appeared to be able to affect a large part of the ureter simultaneously. The jet wave extended further in an anastomosed ureter than in an intact ureter, the apparent reason for this being that fluid transport is facilitated in the permanently open anastomosis tube. The bolus jet waves increased in amplitude with decrease in the distance between the site of contraction and that of the pressure measurement. The action potential appeared during the last, or in rare cases the penultimate wave. Fig. 13 shows the ureteric activity before (13 *a*) and after (13 *b*) anastomosis. Before the transection the contractile frequency of the proximal part of the ureter was twice that of the distal part. This may possibly have been due to insufficient stimulation (less pronounced dilatation phases) every alternate period or to the fact that distally the ureter was refractory. After anastomosis the frequencies were the same in both parts. All contractions were propagated and each complex included a small and a large bolus jet wave and analogous dilatation phases (13 *b*).

The contraction frequency at low intraureteric pressures

It was a general condition that with low intraureteric pressures a sufficiently large bolus jet wave and/or dilatation had to appear in the distal ureteric stump to provoke a contraction there. If the contractions proximal to the anastomosis only gave small bolus jet waves or moderate dilatations of the wall, no contractile response was obtained. In nine experiments, with basal pressures between 0 and 10 mm Hg, a pressure wave of sufficient magnitude was obtained at each proximal contraction to provoke contraction in the distal stump. The peristaltic waves were thus seen to propagate unhindered over the anastomosis (Figs. 14 and 15). Fig. 14 shows the recordings from intact ureters. Dilatations and also very large bolus jet waves were observed at all measuring sites before the contractions. Fig. 15 shows the sequences from the same experiment after anastomosis; lower frequencies and marked respiration-dependent artifacts are seen.

In four cases the frequency was higher in the proximal part and contractions occurred distally only after large bolus jet

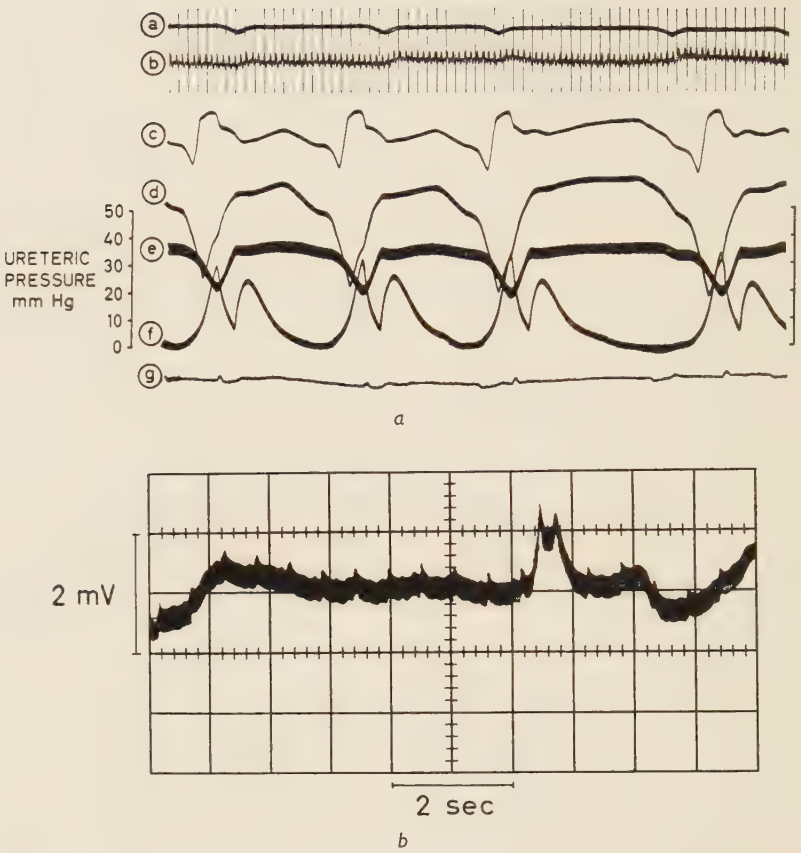


Fig. 14. Peristalsis in a ureter with intact pelviureteric connections. From above, the time marking in seconds, respiration (*a*), arterial pressure (*b*) (mean pressure 150 mm Hg), *diameter recording from three sites:* (*c*) nearest to the kidney, (*d*) 23 mm distal to (*c*), and (*e*) 38 mm distal to (*d*), ureteric pressure (*f*) and *electromyogram* (*g*). (*e*) and (*g*) were recorded at the same level. The appearance of the action potential can be seen best on the oscilloscope picture (14*b*). The regular small disturbances in the electromyogram are due to a superimposed electrocardiogram.

waves and/or dilatations. Intermittently the contractions were propagated so that the frequency ratios were 2: 1, 3: 1 or 4: 1.

The contraction frequency at high intraureteric pressures

At high basal pressures (15–30 mm Hg) the correlation between the activity in the two ureteric segments obviously dete-

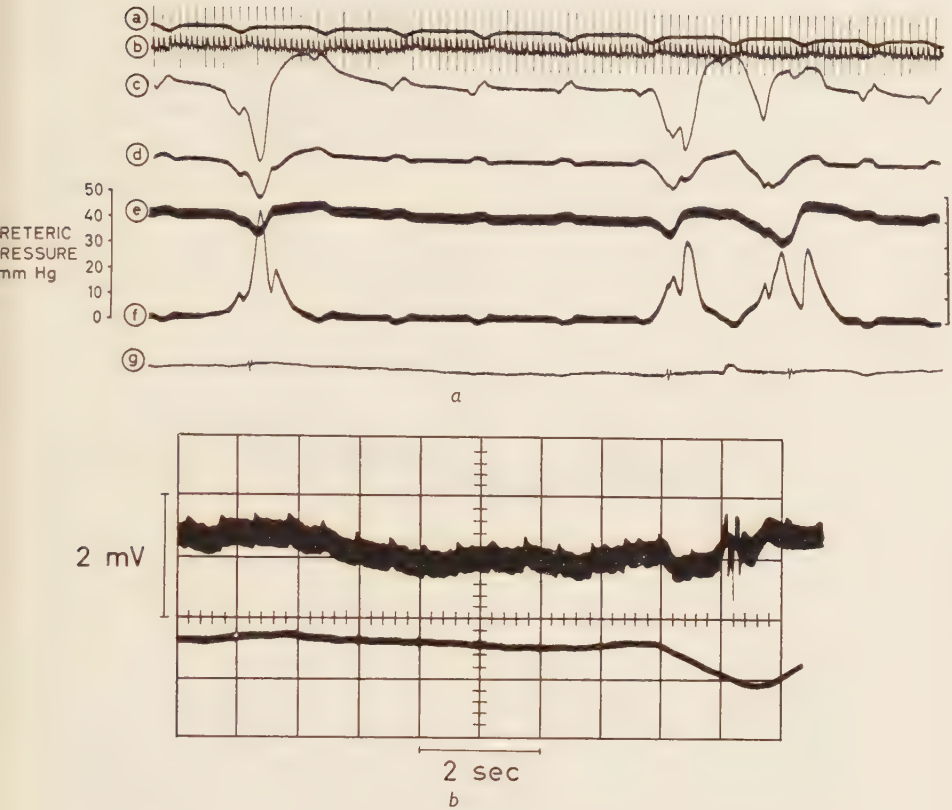


Fig. 15. The same experiment as in Fig. 14 after transection and re-anastomosis between (d) and (e). The notation is as in Fig. 14*a*. The oscilloscope picture (15*b*) shows the electromyogram (above) and diameter measurements from site (*e*). It is evident that the action potential appears during a dilatation phase. The electrocardiogram is superimposed. The second contraction in Fig. 15*a* seems to arise from a site near the anastomosis [late dilatation phase in curve (*c*)] while the third contraction starts proximal to (*c*).

riorated and the distal stump functioned more or less independently. Both high and low frequencies were noted in the distal part but lower frequencies were more predominant than in the proximal region. A proximal contraction was still able, however, to function as a trigger for the distal part (Fig. 16).

At high basal pressures a volley of contractions was sometimes provoked distally. A new action potential appeared here at the end of a contraction and at the end of the new contraction a further action potential appeared, etc. Every pressure wave, how-

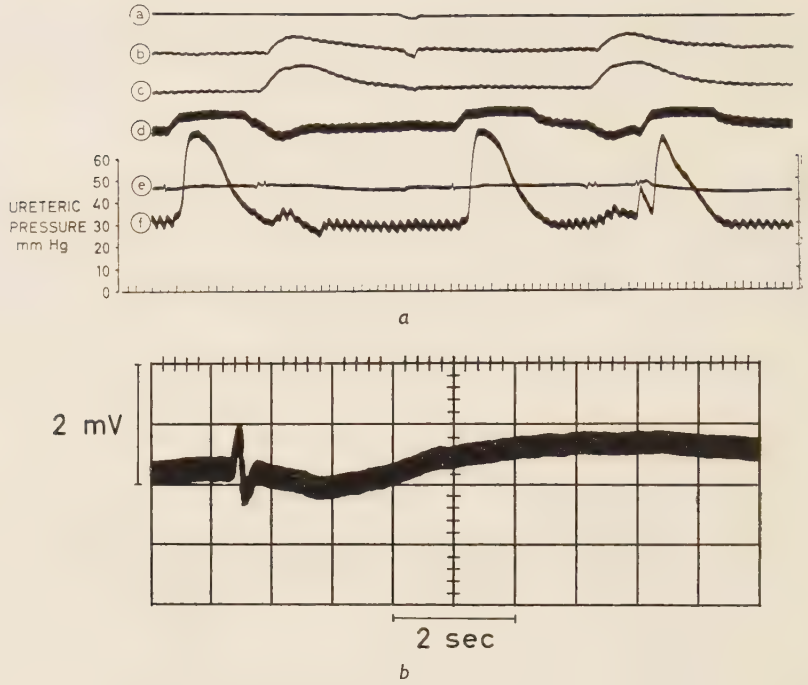


Fig. 16. The activity in a re-anastomosed ureter with high intraluminal pressure. In Fig. 16*a* are seen from above, respiration (*a*), proximal diameter (*b*), diameter just above anastomosis (*c*) and below anastomosis (*d*), electromyogram (*e*) and ureteric pressure (*f*). Below, time in seconds. There are three contractions in the lower segment but only two in the upper. During both (retrograde?) contractions in the upper segment the lower segment dilates and the pressure rises. But only with the second contraction is the stimulation adequate to excite the lower segment. Fig. 16*b* shows the oscilloscope picture of a simultaneous action potential.

ever, had a lower amplitude than its predecessor, and finally the contractions faded out.

Signs of retrograde peristalsis were observed on several occasions. In particular a stimulus wave seemed to be able to turn at the anastomosis, but antiperistalsis produced from the distal part could also occur after a normal peristaltic wave had turned at the distal ureteric catheter.

The velocity of the contraction waves

The propagation velocity was similar to that found earlier, but varied over a somewhat greater range, i.e. 9–24 mm/sec

instead of 12–20 mm/sec. As a rule the velocity between the proximal and intermediate indicators appeared to be the same as between the intermediate and distal indicators (across the anastomosis). Occasionally propagation was more rapid across the anastomosis. Velocity determinations could only be made when clear contractions were recorded at all measuring points. This required an intraureteric pressure of more than 10 mm Hg, which was reached in only eight cases. At low pressures the contractions are not manifested as diameter reductions. This has been discussed in more detail in chapter IV.

Discussion

The regulation of ureteric peristalsis

The question of the nature of propagation in smooth muscle has been extensively investigated. Different types of organs have been studied (oesophagus, taenia coli, uterus, vascular walls, ureter, *inter alia*) with different techniques. Opinions have varied regarding the importance of an autonomous innervation in the case of the ureter, but the majority oppose the view that ureteric peristalsis is governed or influenced by autonomous nerves (Engelmann 1869, Bozler 1938, Davalos 1947, Lapides 1948, Morales *et al.* 1952, Risholm 1954, Sleator and Butcher 1955, Corey *et al.* 1956, O'Conor and Dawson-Edwards 1959, O'Conor 1961, Melick *et al.* 1961 *b*, Hamm and Weinberg 1962). There have been some dissident voices, however. Baker and Huffer (1953) and Gould *et al.* (1955 *a*) considered that the ureter had a double autonomous regulation in which the sympathetic impulses decreased and parasympathetic impulses increased the motility or tone. Hanley (1953) reported in clinical material that spastic ureteritis showed improvement after denervation. Satani (1919 *a*) and Durand and Descotes (1952) demonstrated certain effects of nerve stimulation on the ureter, while Kharitonov (1957) claimed he was able to inhibit ureteric peristalsis neuroreflexly. There seem to be no advocates at present for the theory of a *humoral* regulation of the ureter. The question of mechanical extension or stimulation from cell to cell has been discussed with great interest, and evidence for the occurrence of

both types of stimuli has been claimed. It has often been postulated that the smooth muscle cells in the ureter form a sort of syncytium. It has also been suggested that an excitatory stimulus passes between the cells over intercellular bridges (Baker and Huffer 1953). Bergman (1958), in an electron microscopic investigation of the ureter in white rats, found intercellular bridges, which he believed could transmit stimuli between the cells. The smooth muscle of the ureter would thus constitute a *functional* syncytium (Bergman 1958). The modern theories for conduction are discussed in more detail in chapter VI.

The results obtained from investigations of smooth muscle do not provide an unequivocal answer to the question regarding the propagation of stimuli, but the microscopic structure of the ureter seems to provide a possible basis for electrical activation from cell to cell. *The present investigation shows, however, that mechanical stimulation alone is sufficient to propagate a peristaltic wave over an interruption in the continuity of the ureter.* There seems, further, to be a relationship between the magnitude of the stimulus and the response produced, since a stimulus that is too small results in no contraction. This conclusion has been drawn previously (Protopopow 1897, Anderson 1951, *inter alia*). The fact that a peristaltic wave can fade out in the ureter can also be explained in this way. This has been especially observed where a pool has formed in the ureter and where an incoming urine bolus is not always able to provoke a contraction, but where the whole pool sometimes empties (Gould *et al.* 1955*b*). Kiil (1957) described similar findings in man. He considered it possible that the contraction in a pool differs from an ordinary peristaltic wave, and that a distension of the pool can provoke a contraction that empties the whole pool. Murnaghan (1958) also held similar views. The ureter, regarded as a unit, should thus be able to function according to the all-or-none law although the individual muscle cells probably do not function in this way.

The peristalsis in anastomosed ureters

In other investigations also with anastomosis of the ureter the results seem to fit in with a hypothesis that conduction is de-

pendent on mechanical stimulation. If an adequate healing time is taken into consideration, the results have shown that propagation can occur unhindered over an anastomosis. Weinberg and Siebens (1958) in electromyographic studies of the peristaltic frequency before and after transection and end-to-end anastomosis found a considerably lower frequency distally immediately after the anastomosis had been performed. On examination 4–8 months later no obvious difference was seen, and neither was there any retardation across the anastomosis itself, as Butcher and Sleator (1956) claimed after similar experiments. The reason for the lower ureteric activity immediately after transection must be due at least partly to non-specific factors, e.g. tissue oedema, haematoma and obstruction, which prevent the passage of urine and render impossible adequate distension distally. The importance of careful surgical technique to avoid strictures was pointed out by Davalos (1947), among others. The frequently observed finding of moderate hydronephrosis proximal to an anastomosis during the first 2–3 weeks post-operatively before the return of adequate peristalsis may possibly be due to mechanical obstruction during the healing period. The role of stenosis in the occurrence of hydroureters was discussed by Iselin (1929), who considered that *the stenosis and not the discontinuity in the musculature was the deciding factor*. Mobilization of the ureter has also often been described as sufficient to temporarily inhibit the ureteric activity and may probably contribute to an initial reduction in peristaltic frequency.

Weinberg and Siebens attempted to explain the retardation across the anastomosis found by Butcher and Sleator in their chronic experiments, by differences in surgical technique. There was also another difference. Butcher and Sleator stimulated the ureter with an intraluminal balloon, and there was no fluid available to distend the ureter distally to the anastomosis. It seems plausible that in a scarred and empty ureter with muscular discontinuity the contraction wave will be delayed in the region of the scar. If there is, however, a fluid bolus advancing in front of the contraction wave, this should be able to activate the muscles on the other side of the scar, thus perhaps eliminating the contraction delay.

Benjamin *et al.* (1956) carried out a series of anastomosis ex-

periments with a polyethylene tube 5 cm long. A defect was either bridged with the tube alone or half of the circumference of the ureter was retained. After healing, contractions were observed both above and below the defect in both types of experiment. No synchronization was found, however, between the two parts of the ureter. If the conduction were purely myogenic, at least some of the contractions should have been propagated in those cases where half of the ureteric circumference remained. Experiments with trans-sectioning of half of the circumference were also reported by ALKSNE (1907), who found that a contraction ceased at the site of incision if the latter extended into the lumen but continued unhindered if the mucosa was intact. WEINBERG (1962) made a corresponding observation on the relationship between flow and activity in studies of the peristalsis after diversion of urine through a vertical ureterotomy. WEINBERG recorded electromyograms both proximally and distally to the ureterotomy and found that action potentials appeared only proximally, while the distal part, to which no urine penetrated, remained inactive. WEINBERG found a return of normal peristalsis after healing. If the conduction takes place only by means of myogenic spread, a linear vertical ureterotomy should not have a blocking effect.

The effect of dilatation proximally to a stenosis

In the anastomosis experiments of BENJAMIN *et al.* described above, a dilatation was recorded in the upper ureteric segment. BENJAMIN considered that there was flow resistance in the rather narrow prosthesis. *It is conceivable that in situations with ureteric dilatation proximally to a stenosis or other forms of flow impediment a damping occurs such that with the proximal contractions a bolus jet wave sufficiently large to excite the musculature does not reach the post-stenotic region.* Perhaps not until a certain degree of fluid filling occurs in the distal segment is there sufficient distension to provoke a contraction. An apparent inactivity might thus be due to mechanical factors and the ureter would be assessed as atonic since the proximal contractions were masked by damping and the distal contractions were only seldom provoked.

The importance of regenerative power to ureteric function after anastomosis

The ureteric muscles have been considered to have good regenerative powers, especially if there is some form of contact between the cut surfaces. The good results obtained after long periods of observation could therefore be due to complete healing in the operation region, but good propagation has also been demonstrated when prostheses separate the sectioned surfaces. Studies of the power of regeneration in the ureter were made by Oppenheimer and Hinman (1955) and Hinman and Oppenheimer (1956), *inter alia*. They found good healing in parts where half of the circumference had been excised, and it was best if no splint had been used. The mucosa regenerated within a week, and the smooth muscle within 4–6 weeks. The flow of urine through the operation region delayed healing. Similar results were obtained by Deniz *et al.* (1962), who found good but not complete healing of the circular musculature and also that free urinary flow could cause extensive fibrosis. Hamm and Weinberg (1956) performed experiments with linear ureterotomy and other longitudinal defects, and also found good healing. Kočvara and Žák (1962) obtained good healing in dog ureters with teflon prostheses, and in cases in which a central ureteric segment had been substituted a normal ureteric passage was also evident on excretoric urography, after transient reduction in function and stasis, as well as normal ureteric dimensions both above and below the prosthesis.

In man observations have been made mainly during operations on hydroureters. Melick *et al.* (1962) observed that with low pressure and pronounced dilatation human ureters, after transplantation from bladder to skin, re-acquired normal size and regained reasonably normal intraureteric pressure in a number of cases. Swenson and Smyth (1959) made similar findings on children with megaloureters. After cutaneous ureterostomy aperistaltic ureters to a large extent regained good peristaltic function. The likelihood of this occurring can depend on the pre-existing degree of ureteric enlargement (Swenson *et al.* 1959).

In spite of the good power of regeneration in the smooth muscle of the ureter, complete healing has never been described. According to Iselin (1929) and others, this is not, however,

necessary for good peristaltic function. The results of previous investigations with prolonged experiments without more severe grades of stenosis should therefore, in principal, be similar to those of the present acute experiments. Difficulties with regard to the blood supply in these latter experiments seem to have as their counterparts the stenosis, dilatation and other disturbances in short term chronic experiments. The circulatory disturbances as a rule probably have only a transient effect on ureteric function, even if in acute experiments they can render the observations impossible. The blood vessels running along the ureter should, however, be adequate for the nutrition of a stripped or transplanted ureter (O'Conor 1961).

Changes in function due to transection

In the anastomosis experiments the principal findings were the same as with intact ureters (chapter IV). *It is clear that depolarization in the muscle cells occurs at the same time as and is dependent on the distension, regardless of whether the peristaltic propagation is provoked mechanically and/or syncytially.* The trigger effect represented by the extension of the ureteric wall must be sufficiently large on anastomosis to prevent a peristaltic wave from fading out. Whether a presumptive propagation from cell to cell changes the sensitivity to the trigger effect, and thus an anastomosis would reduce the excitability, cannot be determined from the present study. In most cases the lower segment had the same peristaltic frequency as the upper, both before and after transection and anastomosis; in other cases the activity was reduced distally after the division. Operational trauma certainly plays some part, but it is highly probable that the ureter functions more satisfactorily if there is physiological contact between the muscle cells. An example of this was seen in the perfusion experiments on rabbits, discussed in chapter II, where the peristalsis deteriorated considerably when the ureter was divided at the renal pelvis. The sensitivity can probably vary both between different parts of the ureter and between different animal species.

The passage of fluid through the anastomosis tube

The insertion of an anastomosis tube that keeps a part of the ureter open, even when no fluid is distending the lumen, can

have several effects. As mentioned in chapter II, the local static tension in the wall at the place of insertion of the tube might be expected to result in the appearance of spontaneous propagated contractions even at low intraureteric pressure levels. This was not observed in the present series of experiments. An open communication should allow more rapid passage of fluid and at the same time result in a pressure effect over a larger part of the ureter than when the urine bolus itself has to open the lumen as it progresses along the ureter. The existence of several bolus jet waves, preceding a contraction, showed that the latter effect occurred. Each bolus jet wave was more extensive and a summation was obtained in certain cases with 2–3 successively higher pressure steps in the ureteric pressure recording. The correlation between the proximal contraction and the passage of the dilatation and bolus jet wave distally was good, and well illustrated the origin of this pressure increase.

As regards the more rapid fluid transport through an open tube, there was a greater velocity of the bolus front across the anastomosis in a few experiments. The anastomosis tube, however, cannot be dilated by the passage of fluid, and if a large bolus is to be pressed forward it is not certain that the open rigid connection has always a lower resistance to flow than an elastic-walled organ which is initially closed. Furthermore, the number of observations giving indirect information on this point was very small and the sensitivity of the diameter indicators somewhat inadequate, so that with regard to the divergent results no definite conclusions can be drawn.

At high intraureteric pressures the correlation between the contractions on either side of the anastomosis deteriorated. The two ureteric stumps contracted to a large extent independently of one another, and it would seem reasonable to assume that the intraureteric pressure was the provoking factor. If the prevailing conditions are sufficient for stimulation no extra pressure increases are required in the form of a bolus jet wave to provoke activity, and the frequency then becomes dependent on the strength of the pressure stimulation and the condition of the ureter. In an intact ureter, however, it is not presumably advantageous to have different frequencies in different parts of the ureter. As has been described in chapter III no frequency

difference was found in the experiments with high pressure and free pelviureteric communication in the few cases where several diameter indicators were used. The fact that the frequency is the same at different levels in an intact ureter is probably due to the fact that somewhere in the musculature there is a pacemaker, the frequency of which dominates the entire organ by the physiological connection between the muscle cells. If the ureter is divided by an anastomosis the muscular connection is interrupted, and an impulse emanating from the pacemaker cannot directly bridge the anastomosis. If the ureter is dilated and the intraluminal pressure high, a functional pacemaker may then be present in each part of the ureter. It is highly probable in this case that the frequencies differ, since the spontaneous contraction frequency has been found to be different in different parts of the ureter (Shiratori and Kinoshita 1961 *b*, and others). In agreement with this, different frequencies in both parts of the ureter were also recorded in the present anastomosis experiments with high pressures.

As in the series of experiments described in chapter IV signs of antiperistalsis were observed. No decisive evidence of this was obtained, however, since neither electromyograms nor pressure were recorded in the upper part of the ureter. In experiments with pig ureters, however, Melick *et al.* (1961 *a* and *b*) showed that normal peristaltic propagation could be obtained in a ureter even when a segment had been excised, subsequently reversed in direction and re-anastomosed. Thus in the transplanted segment the contractions moved in an opposite direction to the pre-operative contractions in that segment, and the ureter functioned well. For a definite solution of the problem regarding the occurrence of antiperistalsis under different conditions, further investigations are required with measurements at several points of the electromyogram, diameter and pressure.

CHAPTER VI

The conduction mechanism in the smooth muscle of the ureter

As is evident from the discussions in chapters IV and V, there is some disagreement as regards the conduction mechanism in the ureteric musculature. No general rules for conduction in smooth muscle can be laid down, since different types of smooth muscle show obviously different patterns of behaviour. Bozler (1948) classified smooth muscle into two groups: multiunit muscles, in which the conduction was assumed to be transmitted by nerves, and unitary muscles in which the conduction was said to take place by the spread of stimuli from muscle fibre to muscle fibre. The former category includes, for example, the pupillary, ciliary, pilomotor and vascular muscles. There is some disagreement, however, concerning the conduction in the muscles of the vascular walls (Burnstock and Prosser 1960*a*, Roddie 1962*a* and *b*). The visceral muscles are included in the unitary group, but they are not, however, an entirely homogenous group. Thus, for example, the excitability of the uterine musculature is affected by some hormones and the intestinal and the ureteric muscles react differently both to the influence of some drugs and to nervous stimulation. Because of the differences between the various types of muscle, therefore, the following discussion will mainly be limited to the ureter.

Theories regarding the conduction mechanism

According to the four principal current theories, conduction can be mediated by (*a*) nerves, (*b*) transmitter substances liberated between the muscle cells, (*c*) electrical current spread from cell to cell or (*d*) mechanical distortion.

(*a*) *Nerves.* While in older investigations it was considered as a rule that the ureter was governed by nerves, it is now generally

held that the ureteric musculature is fairly autonomous. The "extrinsic" nervous influences on ureteric peristalsis have been discussed in chapter V. As regards the hypothesis that *conduction* is mediated by nerves, this is clearly not supported, for example, by the low propagation velocity and low sensitivity to nerve- and synaptic-blocking drugs (Bozler 1938, Lapides 1948, Sleator and Butcher 1955, Prosser *et al.* 1955, Borgstedt 1960, Mazella and Schroeder 1960). Nerve tissue does exist in the ureter but its role in normal peristaltic function is still unclear.

(*b*) *Transmitter substances.* The question of a transmitter substance has been much discussed in the literature, and attempts have been made to demonstrate its existence. The role of histamine in ureteric function has attracted particular attention (see Borgstedt *et al.* 1962, for further references). Butcher and Sleator (1956), in experiments with re-anastomosed ureters, found a delay in conduction across the anastomosis, which they considered was possibly due to the slowness of penetration of a presumptive transmitter substance through the scar tissue. Butcher *et al.* (1957) also came to similar conclusions.

The occurrence of cholinesterase in the urine has aroused especial interest. Benjamin *et al.* (1956) found higher concentrations of the enzyme in dogs than in man, but no difference between normal and pathological ureters in the same species. de Klerk (1954) also studied the cholinesterase in dog ureters and found that perfusion with a cholinesterase inhibitor could abolish peristalsis. He discussed the existence of an inhibitory substance in the urine and its possible significance in the occurrence of ureteric structures.

(*c*) *Electrical current spread.* A large number of investigations have been performed, especially with isolated preparations and varying electromyographic techniques, in order to shed light on the problem of whether conduction takes place by means of the transmission of action currents from cell to cell. Several workers have shown that electrical stimulation of the ureter provokes contractions (e.g. Engelmann 1870, Bozler 1938, Sleator and Butcher 1955, Ichikawa and Ikeda 1960). It seems reasonable, also, to suppose that the cell membranes might be depolarized by an electric shock.

Two types of transmission are possible. Either the ureteric

muscles constitute a syncytium (Engelmann 1869, Bozler 1938), or the stimuli are transmitted through the intercellular space to adjacent cells. In this case the impulse might either pass over intercellular bridges (=functional syncytium), via overlapping muscle fibers (=ephaptic conduction) or through non-excitable material. The hypothesis that some form of electrical conduction occurs has many advocates (Prosser *et al.* 1955, Bülbring *et al.* 1958, Ichikawa and Ikeda 1960, and others). Prosser *et al.* (1960) showed in comparative studies that there was a clear relationship between the size of the intercellular space and the conduction velocity. The greater the distance between the individual muscle fibres in an organ, the lower was the conduction velocity observed. The excitation should thus be propagated more rapidly if the distance between the cells is small.

Like other visceral musculature, the ureteric muscles exhibit two types of membrane potential variations. Both slow, small potential changes and spike potentials have been shown. The former are accompanied by tone changes in the muscle cell (Bozler 1942 and 1948), the latter by regular contractions. The slow potentials are propagated only to an insignificant degree, and have been related to a pacemaker function (Bozler 1942, Ichikawa and Ikeda 1960, Burnstock and Prosser 1960 *b*, Bülbring 1961, and others). There appears to be no clear idea of the optimal contraction frequency of the ureter. In consideration of the long absolute refractory period of the ureter (1–3 seconds), the characteristic frequency should be fairly low, and it seems in fact to vary within broad limits. Experiments with electrical stimulation reported up to the present time have not cleared up this problem fully. Prosser *et al.* (1955) found that the spontaneous rhythm in the ureter varied and was sometimes higher than that to which the ureter could be driven electrically. The highest frequency that Prosser could get a rat ureter to follow was about 1 c/s.

(*d*) *Mechanical distortion.* There seems to be no doubt that an increase in tension in the ureter is an adequate stimulus for initiating contraction. A large number of investigations agree on this point. Intraluminal balloons and injections of fluid and also pinching and stretching have been used. The same response was produced regardless of the manner of distension. Isolated prepara-

tions also react in a similar way. Several authors have shown that there is a relationship between the degree of tension and the membrane potential in a muscle cell (Bülbring 1955, Burnstock and Prosser 1960 *a*, Gillespie 1962 *a* and *b*). Increased stretching gives (sometimes after an initial, single spike) increasing depolarization, and with sufficiently high excitability the cell discharges, a spike potential occurs and contraction follows. Gillespie (1962 *a*), in experiments with colon muscle, found a depolarization corresponding to 5.5 mV when the preparation was only lightly stretched. This difference from the resting potential in an unstretched state was stated as being statistically highly significant. Burnstock and Prosser (1960 *a*) found the same order of magnitude on depolarization with rapid stretching of the ureter in rats and guinea-pigs. Guinea-pig ureters responded to an extension of 1 mm per 12 mm muscle length. Bozler (1947) investigated the effect of stretching in dog ureters and found that distension above a certain limit provoked slow transient potential changes. The response was related to the distension applied. On further stretching a conducted response arose from the local response.

There thus appears to be a distinct relationship between the degree of stretching in the muscle cell and membrane polarization, and also therefore the excitability, but *the rate at which an increase in tension occurs is probably important.* In model experiments with a pressure-sensitive cell analog which was subjected to one particular pressure rise but initiated with different velocities, Teorell (1959) found that a certain minimal velocity in the pressure increase was required to obtain a potential response. Static and dynamic pressure in the carotid sinus, and also the firing frequency of potentials in the carotid sinus nerve were studied by Warner (1958), who formulated a relationship between these factors.[1] Teorell (1962) examined this relationship

[1] Warner used an electronic analog of the carotid sinus and the following equation was used to describe its function:

$$n = K_1 (P - P_0) + K_2 \frac{dp}{dt},$$

where n is the frequency of action potentials at a point on the carotid sinus nerve, P is the pressure in the carotid artery, P_0 is the minimum *static* pressure capable of eliciting action potentials, and dp/dt is *the rate of change* of pressure in the artery. K_1 and K_2 are constants.

with an analog computer and found that apart from the application of a minimal pressure a certain velocity in the pressure increase (dynamic pressure) was also required to initiate a potential spike. High pressure applied with a velocity that was too low could thus be insufficient, while a lower pressure with more rapid rise sufficed to give a potential spike. One of the aims of the perfusion experiments described in chapter II was to investigate these circumstances in biological material. The velocities chosen here, however, produced no differences in response, which must mean that both lay above the critical threshold. Burnstock and Prosser (1960 *a*), however, observed differences in the response between rapid and slow stretching of smooth muscle.

It is thus clear that increase in tension in the ureter gives rise to increased excitability. Conduction might therefore occur by the mechanism that one cell in contracting distorts an adjacent cell sufficiently for this cell in its turn to be depolarized. It is also possible that the intraluminal rise in pressure occurring distally to a contraction acts as a depolarizing extension (Gould *et al.* 1955 *a*, Hamm and Weinberg 1962, and others). Ureteric muscle contractions without simultaneous fluid transport have been described, however, by several workers, and the passage of urine therefore does not seem to be necessary but is probably responsible normally for a very important part of the distension. The experiments described in chapters IV and V gave clear evidence that adequate distension was required to prevent the peristaltic wave from fading out. The importance of mechanical distortion in the conduction in smooth muscle has been questioned (Sperelakis and Prosser 1959, Burnstock and Prosser 1960 *b*). The knowledge of the effect of distortion on the excitability makes it difficult, however, to minimize the importance of the stimulus produced by an extension caused by contraction of the adjacent cells. The bridges observed between the ureteric muscle cells (Bergman 1958, Prosser *et al.* 1960) might, in consideration of the lack of protoplasmic continuity between the cells, have a high electrical resistance. It must therefore be asked whether such connections can in fact constitute a transmission path for action currents. It is not precluded that these bridges may be purely mechanical connecting links (Prosser *et al.* 1960).

The relationship between electrical transmission and mechanical distortion

It must be considered proven that electrical transmission can take place between the cells. It is reasonable to assume, however, that it is not solely responsible for the conduction in the ureter. The phenomena of frequency differences, pool formation and inactivity at low pressures support this hypothesis. An electrical impulse alone often seems to be insufficient to depolarize the cell membranes to such a degree that a spike potential occurs, and the contraction wave then dies out. *For the persistence of normal propagation, therefore, a simultaneous mechanical component is probably required.* This mechanical component involves an adequate degree of stretching, provided this stretching takes place at a sufficiently rapid rate. The degree of stretching caused by a given stimulus (a urine bolus or stretching from the adjacent cells) is dependent on the tone of the individual ureter and its power to change the volume for a given tension increase. That which may be an adequate stimulus in one case can possibly be below the stimulation threshold in another. The magnitude of the static pressure induced seems to be of the greatest importance here, since the perfusion experiments described in chapter II allow us to suppose that the threshold rate of the pressure increase does not need to be fast and is probably usually attained.

The view discussed above is similar to that of Burnstock and Prosser (1960 *b*). They concluded that propagation in smooth muscle depends on more than one factor. They considered that the transmission seems to be electrical but propagates best if the muscle has become excitable by stretching or chemical transmitters. The results of the present experiments are not in disharmony with this view. The required excitation is apparently obtained by distension provoked by the bolus jet (or at higher intraluminal pressures by the prevailing tension in the wall). Under special conditions—the anastomosis experiments—it was shown that the distension alone, without obvious delay, was capable of provoking a continued contraction wave. The fact that direct muscular continuity normally plays a part in the propagation, however, was indicated by the lack of contraction asynchrony at

high intraureteric pressures when the ureter was intact, whereas on the other hand different frequencies were recorded in the different segments after anastomosis. *The regular activity in the intact ureter could thus be due to spike potentials, emanating from a pacemaker somewhere in the organ, and propagated along the ureter as long as this is made excitable by adequate distension.*

General summary

The aim of the present work was to study the relationship between the intraluminal pressure and the contractility in the ureter. Dogs were used for the experiments. The effect of different high intraureteric pressures was studied on ureters *in situ* both with perfusion methods and with retention of the physiological connection between the renal pelvis and the ureter. A series of experiments with transection and re-anastomosis of the ureter was performed in order to study the propagation mechanism of the peristalsis.

Chapter I. Introduction

A short history of the physiology of the ureter is presented, and some general problems of interest to this investigation are mentioned.

Chapter II. Perfusion of the ureter in situ

For measurement of the intraluminal pressure a polythene catheter was inserted distally in the ureter close to the urinary bladder. The ureter was totally occluded and the peristalsis was studied. An attempt was made to obtain an intraluminal pressure of more than 25–30 mm Hg, and diuretics were given when necessary. With a progressively increasing intraluminal pressure above 15–20 mm Hg), the contraction-dependent pressure variations in the ureter decreased gradually and finally became immeasurably small. In a second part of the experiments perfusion was carried out via a polythene catheter which was inserted into the ureter near to the renal pelvis. There was thus no fluid communication between the pelvis and the perfusion system, but the nervous and vascular connections between the pelvis and the perfused ureter were left as intact as possible. The perfusion pressure was raised at two constant rates, first at 0.97 mm Hg min and subsequently at 6.05 mm Hg min. The ureteric peristalsis started at pressure levels between 1–2 and 16 mm Hg.

There was no difference in the stimulation effect between the two rates of pressure increase used.

The contractile power at intraureteric pressures higher than 15–20 mm Hg was studied by increasing the perfusion pressure up to a maximum of 155 mm Hg. *Pressure variations due to contractions were shown up to 125 mm Hg.* The degree of damping in the perfusion system could be decreased intermittently, the amplitude of the pressure waves thereby always increasing. It was concluded that *if a ureter with intact connection with the pelvis dilated after obstruction to such an extent that open fluid communication with the pelvis and therefore regurgitation occurs, the peristaltic pressure waves are damped considerably.* In the perfusion system used the degree of pressure damping was fairly low, and the pressure waves could therefore be identified even with very high intraureteric pressures.

Chapter III. The contractility at high intraureteric pressures with intact pelviureteric connections

Ureteric peristalsis was studied in a series of experiments with intact pelviureteric connections. The intraluminal pressure was measured distally after total occlusion, and the electromyogram and ureteric diameter just proximal to the tip of the ureteric catheter were recorded at the same time. On increase of the basal pressure in the ureter the character of the pressure waves changed, and when there was open fluid communication with the pelvis the only important pressure oscillations observed were synchronous with the arterial pulse. Action potentials and ureteric contractions accompanied the peristaltic waves at lower intraluminal pressures. The action potentials and ureteric contractions did not change in character when the pressure became so high that the damping in the pelvis eliminated the pressure waves. The contraction frequency, however, showed a slight tendency to decrease. No relationship between respiration frequency and ureteric activity was shown. It is concluded that *the earlier views that the ureteric contractions cease on high pressure are dependent on the fact that neither pressure measurement alone nor contrast roentgenography is sufficient to demonstrate ureteric activity when the upper urinary tract is dilated.*

Chapter IV. Ureteric diameter variations and electromyograms at low intraluminal pressure levels

Ureteric peristalsis was studied at pressures lower than 15–20 mm Hg and with the pelviureteric connections intact. The ureteric diameter was recorded at two or three different levels and action potentials were measured from a point somewhat proximal to the pressure measurement catheter which was situated distally. The pressure was measured after total occlusion. Diphasic pressure waves as a rule appeared with the peristaltic contractions. The first phase in each pressure wave coincided with a contraction at a more proximal measuring site, and was apparently due to a urine bolus pressed forwards. The forward penetration of a urine bolus distended the ureter, and at the same time an action potential appeared in the dilated region. The second phase in the pressure wave occurred when the muscle contraction reached the measurement site as manifested by a diameter reduction which started after the action potential. When the basal pressure of the ureter became higher the first phase in the pressure wave gradually decreased, and the simultaneous ureteric dilatation also decreased at the same time. The relationship between the pressure waves, diameter variations and action potentials are discussed, and it is concluded that *the ureter probably has to be excited by a certain degree of stretching before a peristaltic wave is able to propagate*.

Chapter V. The peristalsis in an anastomosed ureter

The same technique was used as described in chapter IV. The peristalsis was studied before and after transection and re-anastomosis with a short polythene catheter. The same peristaltic findings with diphasic pressure waves, dilatation–contraction and action potentials were made as described in chapter IV. *After anastomosis of the ureter it was shown that a peristaltic wave could propagate unhindered over the site of division even though there was no myogenous or nervous connection between the two parts of the ureter.* A prerequisite here is that a bolus jet (advancing in front of a contraction wave proximally) should induce a distension, distally to the anastomosis, sufficiently strong to stimulate contraction of the muscles. If the intraluminal pressure

is increased above 15–20 mm Hg spontaneous contractions occur in both parts of the ureter, but the distal part usually has a lower frequency.

The regulation of ureteric peristalsis is discussed, and the effect of an anastomosis examined. Comparisons are made with anastomosis experiments previously reported. The conduction mechanism in the ureter is discussed briefly, and it is concluded that *mechanical distortion plays an important part as regards peristaltic propagation.*

Chapter VI. The conduction mechanism in the smooth muscle of the ureter

The modern theories on the conduction mechanism are reviewed. Experimental data from studies of the ureteric muscles in particular are discussed. It is concluded that the conduction mechanism seems to consist of two components: (*a*) an electrical, and (*b*) a mechanical one. (*a*) *There is probably electrical transmission from cell to cell.* (*b*) *A mechanical distortion of the muscle cells may be required to produce a sufficiently high degree of excitability making possible the electrical transmission.* The way in which this distortion is produced in the ureter with normal peristalsis and at raised pressures is discussed.

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